Diabetes in the older person

Jonathan Hewitt

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Department of Epidemiology and Population Health

London School of Hygiene and Tropical Medicine

Keppel St

London WC1 7HT

Abstract

Background

More people are being diagnosed and treated for diabetes who are aged over 75 years. Compared to younger diabetic populations there is less published evidence available in the older person. At the extremes of old age the evidence base is even smaller.

Aim

To examine several aspects of diabetic epidemiology in the older person in order to expand the evidence base for practice and policy.

Methods

People with diabetes were identified from a representative community based sample of 15095 people aged at least 75 years old. Associations between diabetes and its end points were identified. Admission to hospital and death were assessed in an older diabetic population.

Results

There were 1177 people identified with type 2 diabetes giving a prevalence of 7.80% (95% CI, 7.11-8.47). The prevalence of diabetic complications of poor vision, proteinuria, raised creatinine, angina, myocardial infarction, cerebrovascular accident and foot ulceration were all increased in the diabetic population. Older diabetic people demonstrated a good uptake of diabetic services including regular eye examination, annual chiropody and dietician attendance. However, the understanding of daily diabetic management was poor with a high prevalence of cognitive impairment (22.5%) in the diabetic population. The rate of admission to hospital and length of hospital stay were increased in the older diabetic person compared to the non diabetic person; rate ratio for admission, 1.31 (95% CI, 1.23-1.39) and the length of stay 13.9 days versus 12.4 days, p<0.001. Finally, the risk of death among people with diabetes was higher than for people without diabetes, hazard ratio 1.50 (95% CI, 1.38-1.65), p<0.001. The hazard ratio was similarly raised in both men and women with diabetes across the age ranges studied.

Conclusion

This thesis presents the largest community based study in the older diabetic person. Diabetes was shown to contribute to morbidity and mortality until the extremes of old age.

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Declaration by Candidate

I have read and understood the School's definition of plagiarism and cheating given in the Research Degrees Handbook. I declare that this thesis is my own work, and that I have acknowledged all results and quotations from the published or unpublished work of other people.

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Chapter 1. Introduction

1.1 Diabetes mellitus, a disease overview

1.1.1 History of Diabetes and terminology

The first description of diabetes mellitus occurred in 150 BC by the Greek writer Aretaeus, in his work 'On the Causes and Symptoms of Chronic Diseases'(1). He described thirst, polyuria and dehydration. Around 500 AD Brahmin writers in India noticed the sweetness of urine as insects were attracted to it. They described two forms of the disease. A serious fatal condition occurring in childhood and an adult form associated with obesity(1). The condition continued to be described throughout the following centuries with the 17th century English physician Thomas Willis describing diabetes mellitus as the "pissing evil"(1). Increased knowledge of glucose metabolism and pancreatic function improved understanding of the disease over the next 250 years. In 1921 Banting and Best discovered and isolated insulin in Toronto, Canada. The first use of insulin on a human patient occurred in 1922 by Professor J.J.R. MacLeod, who was in charge of the Canadian team. It became obvious that repeated injections were required and modern diabetology was born. Work by Frederick Sanger in the 1950s revealed the protein structure of insulin which allowed different preparations of the drug to be produced improving its efficacy. In 1982 human insulin became the first genetically engineered drug to be licensed in the world. Oral preparations of drugs which stimulate insulin production have been used in diabetes since the 1950s. In combination with other newer oral drugs and insulin the treatment options for diabetes mellitus have and continue to increase and improve.

A separate, much rarer disease exists called diabetes insipidus. This is not related to diabetes mellitus, although like diabetes mellitus, the condition results in large urine volumes if left untreated. Hence diabetes insipidus derives its name from the same Greek origin as diabetes mellitus. This thesis did not consider diabetes insipidus further. For ease of reading, diabetes mellitus has been referred to simply as diabetes for the rest of this thesis.

1.1.2 Aetiology of diabetes mellitus

Diabetes is a broad diagnosis resulting from a deficiency of insulin, either absolute or relative, which in turn causes high levels of blood glucose. Shared symptoms arise as a result of abnormal glucose levels.

Diabetes can be partitioned into type 1 and type 2 (although there are related conditions such as Gestational diabetes, which were not considered further in this thesis). Type 1 diabetes results from an absolute lack of insulin. It occurs in early life or early adulthood. It is believed to be caused by auto-immune destruction of the β islet cells of the pancreas, which produce insulin.

Type 2 diabetes tends to occur in middle age and beyond and worsen over time. The initial defect is thought to be an increased resistance to insulin in the peripheral tissues and an increased secretion of insulin. Insulin resistance continues to worsen over time. When the maximal insulin secretary capacity has been exceeded, any further increase in blood glucose causes a decline in insulin generation. Possible mechanisms for the decline in insulin secretion include chronic β cell failure and high levels of glucose itself causing toxic damage to the β cells. Eventually this may result in an absolute failure to secrete insulin. The combined affect of increasing insulin resistance and gradual failure of insulin secretion causes raised glucose levels and type 2 diabetes mellitus.

For more detail on the exact definition of diabetes mellitus including the World Health Organisation (WHO)(2) and American Diabetic Association (ADA)(3) definitions please see chapter 3.3.1 below.

1.1.3 The epidemiology of diabetes mellitus

As a proportion of all diabetes, type 1 and type 2 diabetes are 5-10% and 90-95% respectively(4). Both are increasing in prevalence in both the western and the developing world(5). The reasons for the increasing prevalence of type 1 diabetes are unclear. Factors contributing to the increase in type 2 diabetes include: increasing levels of obesity, the aging population and to a lesser extent the improved survival of those currently diagnosed with diabetes(5;6). In the UK the prevalence of type 2 diabetes is estimated to be around 1% of the total adult population(7), however, up to a further 3% of all adults who have diabetes remain undiagnosed in the community(8). Diagnosis is often made by chance in asymptomatic individuals(4). This may be as part of routine testing by health professionals or health screening, for example for life insurance. There are no national screening programs for diabetes mellitus in the UK. In America, the ADA have suggested three yearly screening for adults over 45 years old(9), despite evidence to suggest that opportunistic screening can have a poor yield(10). Screening for diabetes is more cost-effective if targeted at people with hypertension(11), although overall benefit, frequency and method of screening are yet to be firmly established(12).

Two clinical epidemiological trials regarding diabetes are of particular significance and warrant discussion. The first is the Diabetes Chronic Complications Trial (DCCT) from America(13) and the second is the United Kingdom Prospective Diabetes Study (UKPDS) co-ordinated in Oxford, England(14). The DCCT trial recruited 1441 younger individuals, aged 13 to 39 years with type 1 diabetes and was the first trial to conclusively prove that reducing blood sugar levels prevented microvascular complications but with a higher incidence of hypoglycaemia(15). The UKPDS recruited 3642 people with type 2 diabetes, aged between 25 and 64 years. It involved a complex design evaluating many different aspects of diabetic care. It resulted in the publication of numerous landmark papers including the reduction of microvascular complications with improved gylcaemic control, evaluation of different treatment regimes and highlighted the importance of hypertension in diabetic individuals. Many of the different papers published from the UKPDS have been quoted throughout this thesis.

1.1.4 Treatments used in diabetes mellitus

Type 1 diabetes requires the administration of exogenous insulin via subcutaneous injection. Type 2 diabetes can sometimes be controlled with diet and weight loss; restricting the glucose intake and allowing the available insulin to go further by having less tissue mass to work on. Adipose tissue is implicated in increased insulin resistance and decreased insulin sensitivity. If this approach does not control the disease, oral medication may be prescribed. Oral hypoglycaemic drugs work by either stimulating the pancreas to produce more insulin or restricting glucose uptake from the alimentary tract and liver. Within the last decade newer medications have become available which increase the sensitivity of peripheral tissues to respond to insulin. If these measures are not successful people with type 2 diabetes may require the use of insulin to maintain adequate blood sugar control.

1.1.5 Complications of diabetes mellitus

Like most major diseases diabetes is a condition which contributes to co-morbidity as well as causing specific complications. For example, people with diabetes are more likely to fall, be socially deprived, have disabilities or suffer poor health. However, much of this co-morbidity is caused by specific problems relating to diabetes. These are now discussed in detail.

The specific complications of diabetes are numerous and there are a number of methods of classifying them. One method is to divide them into acute and chronic complications, according to the timescale over which the complication occurs.

1.1.5.1 Acute complications

Acute complications result from either a lack of insulin or an excess of insulin. An acute lack of insulin causes an acute metabolic derangement. In type 1 diabetes, the absolute lack of insulin causes blood glucose to rise. The resulting metabolic derangement occurs over a short time, usually 2-3 days and is often how the disease first presents to medical attention. Type 1 diabetic individuals who control their disease poorly, either due to concurrent illness or inadequate insulin administration are also prone to this acute metabolic state. A rarer scenario is the acute metabolic derangement seen in type 2 diabetes, where a relative lack of insulin causes patients to develop a similar but not identical, metabolic state, over a longer time period, which can be up to several weeks. Both of these conditions are serious with high mortality but do not affect the majority of those diagnosed with diabetes who are able to control their disease correctly.

An acute excess of insulin causes a low blood sugar or hypoglycaemia. Within the context of diabetes, an excess of insulin is caused solely by the medication used to treat the condition. As diabetes results from a lack of insulin and subsequent high blood sugar, the main treatment options are based on replacing insulin or stimulating the pancreas to produce more insulin. Maintaining the blood sugar as near physiologically normal as possible is the best way of preventing chronic complications and so every attempt is made to keep the blood sugar as near normal as possible. In so doing, it is common to cause the blood sugar to drop below physiological levels. It happens within minutes and is potentially extremely dangerous. Once the symptoms are recognised by an individual it can usually be easily and quickly reversed by either eating, consuming drinks containing glucose or the administration of intravenous glucose.

1.1.5.2 Chronic complications

Chronic complications affect both type 1 and type 2 diabetic individuals(4;16). They are the result of a chronically high and physiologically abnormal glucose regulation. They occur over a longer time period, often many years. They can broadly be divided into two groups; microvascular complications, which affect the smaller blood vessels in the body, and macrovascular complications, which affect medium and larger sized blood vessels in the body.

Superoxide formation, secondary to high glucose within the mitochondrial electron-transport chain, is believed to form an underlying common pathway for the formation of diabetic vascular complications(17).

Microvascular complications are caused by a chronically high blood glucose. In a study of PIMA Indians conducted in the US, baseline glucose levels at the start of 10 years of follow up predicted the development of nephropathy and retinopathy. This population was aged over 35 years(18). Blood glucose levels also predicted diabetic individuals who progressed to nephropathy in a seven year cohort study in the U.S of 232 type 1 and type 2 diabetic people(19). The UKPDS 35 showed that individuals who maintained the lowest blood glucose sustained the least microvascular complications(14;20), although they are at the highest risk of hypoglycaemia(21). Microvascular diseases affect the eye, especially the retina, known as diabetic retinopathy and the kidney, known as diabetic nephropathy.

Macrovascular complications are more complicated and there has been no conclusive evidence that lowering blood sugar prevents macrovascular complications(22;23). It is believed that simply lowering the glucose level does not mimic the physiology of a non diabetic individual(24;25). Even after treatment has begun diabetic individuals remain insulin resistant. Continuing insulin resistance contributes to a reduction in endothelial dependent vasodilatation and vascular smooth muscle vasodilatation in diabetic subjects. Abnormalities observed in nitric oxide controlled pathways have been proposed as mechanisms for these processes (25). Ultimately, diabetic arteries stiffen earlier than non-diabetic arteries(26).

Diabetes is also associated with dyslipidemia(27;28); high triglycerides, high low density lipoprotein (LDL) and low high density lipoprotein (HDL). This poor lipid profile is established as an independent risk factor for medium and large vessel atherosclerotic disease. Finally platelet function is adversely altered in diabetes and individuals are prone to arterial thrombosis(25). It is a combination of these factors which have been proposed for the high prevalence of macrovascular complications even in diabetic people who maintain very good overall control of their blood glucose.

Macrovascular diseases include coronary heart disease, cerebrovascular disease and peripheral vascular disease. While diabetes is not the sole cause of any of these large vessel conditions, it is well established that individuals with diabetes have a greatly increased chance of developing these conditions compared to individuals without diabetes(16).

Central, peripheral and autonomic nerves are also prone to damage in diabetic individuals. This group of conditions are known as diabetic neuropathies. Their aetiology has not been fully established(16) and can not simply be attributed to micro or macrovascular disease. Abnormal glucose metabolism, oxidative injury and vascular insufficiency are all thought to contribute(29). A comprehensive review of epidemiological and trial evidence by Gaster *et al* in 1998 suggested a trend towards greater neuropathy with poor glycaemic control but did not conclusively prove this(30).

1.1.6 Hypertension and diabetes mellitus

Hypertension is common in people with type 2 diabetes(31). Hypertension is now also being recognised as an important factor in the development of both microvascular and macrovascular complications(4;32;33), particularly diabetic renal disease(34) and diabetic eye disease(35).

1.2 Guidelines and recommendations for diabetes care

Due to the importance of diabetes and its impact on health, many national and international recommendations and guidelines have been developed. In the UK some of the most important guidelines exist as part of the National Service Framework (NSF). The NSF is a Department of Health initiative designed to improve health standards in specific areas of care. There are currently nine different NSFs. Three are of particular relevance to this thesis(4;36;37).

- The NSF for diabetes,
- The NSF for older people
- The NSF for renal services

In 1997, the St Vincents Joint Task Force for Diabetes, an international collaboration, identified diabetes in the elderly as an important and growing problem throughout the world; where treatment and care was often inadequate(38). The European Union Geriatric Medical Society (EUGMS) recently published their guidelines for the management of diabetes in the older person(39). This document was written in collaboration with the International Diabetes Federation, the European Associations for the Study of Diabetes and the St Vincents Declaration Primary Care Diabetes Group. It represented a major step forward in the clinical care of the older person with diabetes.

1.3 Diabetes mellitus in the older person

The vast majority of older diabetic individuals have type 2 diabetes rather than type 1 diabetes. This is because of the poor life expectancy of any individual with type 1 diabetes during the earlier part of the 20th century. Insulin did not become available until 1922 before which life expectancy after diagnosis was only 2.6 years for people with type 1 diabetes. Even after insulin's introduction, the life expectancy of a 10 year old with type 1 diabetes in 1938 was still only 39.8 years because diabetic care was still poor compared to todays standards(40).

Medical management of diabetes in the older person often varies(41). This is due to two reasons. Firstly, older people with diabetes are a group who have been under represented in clinical trials and there is a lack of published scientific evidence to guide treatment recommendations. Many major studies of diabetes did not recruit patients over the age of 65 years, including the UKPDS(14). The lack of information increases with age, with little evidence available regarding diabetic people aged 80 years or above. This lack of available information is true for virtually every aspect of diabetes. Common perceptions that treatment is not worthwhile because of the age of the patient, potential difficulties with day to day management and reduced life expectancy, along with the expected time lag to develop complications, may be reasons for the under treatment of the elderly patient with diabetes. If the patient is not symptomatic, either hypoglycaemic or hyperglycaemic, then the existing treatment regime is often considered to be adequate.

If the older diabetic person is to be treated as aggressively as their younger counterparts then it is vital to ensure that definite benefit is conferred by treatment. Hypoglycaemia, adverse drug reactions, the burden of multiple drug treatment and increased anxiety are all potential factors which have been used to argue against more aggressive treatment of diabetes, particularly in those at the oldest ages, though without a good evidence base. Equally if there are indeed benefits of aggressive control of glucose and/or hypertension in older people with diabetes, then they need to be firmly established. The data presented in this thesis would constitute one of the largest self reported studies of diabetes in this age group.

As discussed in this section, the vast majority of elderly people with diabetes have type 2 diabetes. In this thesis all the subjects with diabetes had type 2 diabetes. Therefore for the ease of reading all references to "diabetes" relate to type 2 diabetes, unless specifically stated.

1.4. Thesis Objectives

1.4.1.Objective 1: To establish the prevalence of diabetes and its complications in people aged 75 years and over.

Firstly, the prevalence of diabetes, including previously undiagnosed diabetes and glycosuria was estimated. Following this, the diabetic population was described. The description of the diabetic population included demographic characteristics and social status. Other descriptive factors of interest were socio-economic status, smoking history, alcohol intake and anthropometric data. Finally, microvascular and macrovascular endpoints, were estimated within the study population. The population attributable risk fraction was calculated for each diabetic endpoint.

1.4.1.1 Background

The prevalence of type 2 diabetes has increased in all age groups and populations over recent decades(6). In the older person exact prevalence estimates vary between authors. Variations exist because the age of populations varies between studies, ethnic differences exist, case ascertainment varies and the method of diagnoses of diabetes can vary(42). No U.K. contempory large scale community based population estimates of the prevalence of diabetes in the older person are currently available.

Large well conducted studies, such as the WHO multinational study of vascular disease in diabetes (WHO MSVDD), have established the increased prevalence of diabetic end points in diabetic younger populations(43;44). The prevalence of diabetic end points has previously been assessed in older populations. However, these studies have tended to be small and contained limited information regarding the very oldest diabetic populations.

1.4.2 Objective 2: To describe the management and patient understanding of their diabetes in this age group

For the diabetic participants, the treatments taken for diabetes and who, if anyone, was medically responsible for managing their diabetes were recorded. Next, an estimation of the degree and type of home glucose testing was made. The degree to which additional diabetic services were utilised was then described. The occurrence and management of hypoglycaemia was assessed. Correct management of hypoglycaemia and its avoidance requires a high degree of patient understanding about their condition. Three specific questions regarding the level of understanding were then described for the diabetic population. The final part of this objective was to assess associations of these exposures and the presence of diabetic endpoints.

1.4.2.1 Background

The day to day management of diabetes is largely patient based. Education is recommended for everyone with a new diagnosis of diabetes. Education enables patients to take responsibility for their own care. There are several components of successful, long term, patient based management. These include diet, correct self-medication, monitoring blood glucose and the use of specialties allied to diabetic health care.

Numerous health professionals can be either solely or jointly responsible for a diabetic persons care. This could be the GP, diabetic specialist nurse or hospital specialist. The degree to which the older person sees any of these medical specialists is largely unknown. Diabetes is treated on a multi-disciplinary basis, using hospital and community based specialists to aid individual knowledge and treatment. It is believed that the use of a range of diabetic specialists aids in the overall care of the patient. For example, dieticians provide advice regarding weight loss and suitable diet. Chiropodists aid in foot management in the diabetic person and regular eye screening can detect and treat diabetic eye disease. The degree of utilisation of these different services has not been assessed in a large older age group.

Home glucose testing is designed to maximised a persons ability to mange their own disease; tightly regulating blood sugar while at the same time preventing hypoglycaemia. This thesis provided a description of the level and type of home glucose testing in an elderly group of this age in the United Kingdom. It also provided an estimate of the prevalence of hypoglycaemia in the older diabetic person.

It is likely that some older diabetic individuals have poor understanding of every day management of their condition, exacerbated in those with cognitive impairment. The level of diabetes understanding amongst an elderly population has never been assessed on this scale before. This thesis provides an interesting insight into the degree of understanding of the disease in an older diabetic population and the factors that were associated with it.

1.4.3 Objective 3: Evaluation of the relationship between hypertension and diabetes in this age group.

The next objective investigated the relationship between diabetes and hypertension, both diastolic and systolic, in older diabetic patients. The diabetic hypertensive population was described. Hypertension was then assessed in relation to diabetic end points.

1.4.3.1 Background

The control of hypertension, both systolic and diastolic, is increasingly recognised as being equally and possibly more important than blood sugar control(32;33;45). Increasing amounts of evidence support the role blood pressure plays in the pathogenesis of most diabetic end points, particularly diabetic retinopathy(46) and diabetic renal disease(34;47). The affect of blood pressure in causing diabetic end points was shown convincingly from UKPDS 36 and 38 and from the micro-HOPE sub study of the Heart Outcomes Protection Study(32;33;45). While the affect of blood pressure has been established the exact levels which require treatment are not yet established. (27;33;45). The American Diabetic Association (ADA) currently recommends 130 mmHg systolic and 80 mmHg diastolic as the maximum levels of blood pressure for people with diabetes. The ADA recommends that diabetic individuals, of all ages, with blood pressure readings higher than these levels should have their blood pressure treated. European guidelines recommend less aggressive blood pressure treatment in the older diabetic person and the guidelines make allowances for comorbidity(39). Whether blood pressure has the same associations with diabetic end points in older people has yet to be established, let alone whether specific thresholds for treatment of blood pressure are appropriate. There is some evidence that hypertension at the extremes of old age behaves in a different manner to younger populations(48) and there is currently no consensus regarding the best type of anti-hypertensive medication to use(49).

1.4.4 Objective 4: Evaluation of the relationship between renal function and diabetes in this age group.

This objective involved the investigation of the relationship between renal function and diabetes in an elderly diabetic group. Firstly, the older diabetic population with renal impairment was described. Comparisons of renal function (proteinuria, creatinine measurements and Glomerular Filtration Rate) in people with and without diabetes were then conducted.

1.4.4.1 Background

End stage renal failure is increasing in prevalence(50). Type 2 diabetes has recently become the commonest reason for end stage renal failure and subsequent dialysis in Western Europe(31). The majority of diabetic renal disease shows a similar morphological pattern and disease progression. Typically, larger and larger amounts of protein are lost from the kidney into the urine, eventually leading to impaired renal function and failure(51). Advanced age and male sex have both been identified as non-modifiable risk factors for the progression to end stage renal failure among diabetic people(47). Established modifiable risk factors include elevated blood pressure, albuminuria, proteinuria, poor glycaemic control and smoking(47;52). Once end stage renal failure has developed in patients with type 2 diabetes the life expectancy is very poor(50), with cardiovascular death having a disproportionably high incidence in people with diabetic renal disease(50). There is, however, growing evidence that the progressive renal impairment seen in diabetes is preventable(47). In addition there is evidence to suggest that some medications may prevent onset, and delay progression, of diabetic renal disease(53). This thesis provided an assessment of several of these areas in an older diabetic population.

1.4.5 Objective 5: Comparison of the rate of admission to hospital in an older diabetic population, compared to an older non diabetic population.

This objective undertook to assess and describe the data available regarding admission to hospital; admission rates, number of admissions and the length of stay in an elderly diabetic population.

1.4.5.1 Background

Diabetes has been established as an independent predictor of health care utilisation in adults aged 71 years or older(54). A six year cohort study in America showed that diabetes predisposed to repeated admission to hospital in the same individual. This study used the Medicare program and assessed people aged over 70 years(55). If diabetes contributes to health care use and repeated admission then elderly diabetic patients will have a higher rate of admission to hospital. This thesis provides the opportunity to assess admission rates, the length of stay of participants with diabetes and some of the risk factors for admission to hospital in an older diabetic population.

1.4.6 Objective 6: Evaluation of the affect of diabetes on mortality rates in an older population.

The final objective of the thesis investigated the risk of death; all cause mortality and cause specific mortality (circulatory and renal) in the older diabetic person. The risk of death in diabetic people with renal impairment was also assessed.

1.4.6.1 Background

Although it is likely that diabetes affects morbidity and mortality in the older person, the evidence is sparse. In 1997, Sinclair and colleagues performed a comprehensive literature review of 20 studies(56). They concluded that there was likely to be an association between diabetes and death rates. More recent studies have confirmed the association with mortality and diabetes in the older person(57-60). In general these studies suggest that diabetes remains an important contributor to mortality in the older person, but the extent of its effect declines with increasing age. The limitations of these studies are that they provided little detailed information in the very oldest people and none for diabetic people aged over 90 years and that there is no consensus among them regarding the affect of gender and diabetic mortality.

The predominant cause of excess mortality in people with diabetes is cardiovascular disease(60;61). Cardiovascular death has been estimated to be the cause of death in up to 86% of diabetic people(62). As well as cardiovascular disease being the major cause of death in people with diabetes, diabetes has become a greater contributor to the burden of cardiovascular mortality and morbidity for all adults(63;64). This is due to several reasons. Firstly the increasing prevalence of diabetes. Secondly the rate of improvement in cardiovascular outcome is lower in diabetic individuals than non diabetic individuals(64). Finally diabetes is often associated with multiple cardiovascular risk factors(61) which increase the diabetic individuals risk of cardiovascular disease still further.

In addition to their contribution to end stage renal disease, poor renal function and proteinuria are both independent risk factors for both all cause(60) and cardiovascular mortality(65). It also follows that if diabetes affects renal function, the rate of renal mortality would be raised in the older diabetic person.

It has not been established conclusively whether cardiovascular or renal mortality are increased in the older diabetic person and there is comparatively little evidence of the affect of diabetes at the extremes of age. Neither has the affect of proteinuria or poor renal function in old diabetic people been assessed on a large scale. The associations with death (all cause, circulatory specific and renal specific) and the affect of renal impairment on mortality in elderly diabetic people, many of them very old, were studied in this thesis.

Chapter 2. Methods

2.1 Background

2.1.1 The MRC Trial of the Assessment and Management of Older People in the Community (the MRC study)

Investigators: Professor Astrid Fletcher (London School of Hygiene and Tropical Medicine), Dr Dee Jones (University of Wales College of Medicine), Professor Chris Bulpitt (Imperial College London), Dr Alistair Tulloch (University of Oxford).

Trial steering committee: Professor Sir John Grimley Evans (Chairman from 2001), Professor Sir Andy Haines (Chairman 1994-2000), Professor Carol Brayne, Professor Karen Luker.

Funding for the trial was provided by the Medical Research Council, the Department of Health and the Scottish Office. Local ethics committee approval was obtained for each of the participating general practices.

The data presented in the following chapters was collected as part of the MRC study. It was therefore important to describe the trial in some detail. The trial was a two stage large multi-centre trial involving 106 general practices. The principal objectives of the trial were to evaluate different packages of multidimensional assessment and management of elderly people(66).

Background to the MRC trial

Three studies published in the 1960s and early 1970s identified a high level of undetected disease and unmet social needs in elderly people(67-69). Subsequently six randomised controlled trials were conducted in the late 1970s and 1980s(70-75). Five of these trails were conducted in the UK and one in Denmark. All of them had low power and short follow up time. None of them provided conclusive evidence for regular screening in elderly people, although the Danish trial(72) suggested possible benefits in mortality and admission to hospital. Despite the lack of conclusive evidence, in 1990, the Department of Health introduced an annual screening assessment for anyone aged over 75 years. The annual assessment was very general but some broad areas suggested for evaluation were; sensory function, mobility, mental condition, physical condition including continence, use of medicines and social environment. The screening assessment formed part of the general practitioners contract of service and was thus compulsory.

If disease is detected via a screening program there needs to be appropriate medical management pathways in place to deal with that disease. There is some evidence to suggest that hospital based care may offer advantages over primary care based management. A review of the available evidence and meta-analysis(76) suggested that hospital based multidisciplinary geriatric care offered advantages over other forms of management of older people.

The MRC trial of the assessment and management of older people in the community

In light of this compulsory screening assessment the MRC study was undertaken. Its primary aims were twofold; to determine whether an annual multidimensional screening assessment identified disease in the community and to assess optimal methods of management of disease identified. The MRC study included comparison of multidisciplinary geriatric care (GM) against primary care based treatment (PC). Therefore identification of disease was the first stage of the study and the second stage was the method of clinical management; either GM or PC. There were 52401 people aged 75 or over who were not living in a nursing home and did not have a terminal illness invited to participate. Participants were cluster randomised by general practice to a targeted arm or a universal arm. There was no control group who received no screening whatsoever because an annual screening assessment was a requirement of all GPs and denying anyone a screening assessment was deemed unethical. All participants enrolled in the trial then underwent a brief assessment questionnaire. Following the brief assessment, practices randomised to the universal arm then conducted a detailed assessment. People in the targeted arm only underwent a detailed assessment if they "triggered" predetermined questions deemed to indicate unmet health or social needs. People enrolled into either arm of the trial were then followed for admission to hospital, admission to institutional care, quality of life and death, all of which were primary outcomes of the trial. There were 21128 individuals originally randomised to the universal arm of the trial. It is these people who were considered for this thesis. Individuals originally randomised to the targeted arm did not have data collected relating to diabetes. Individuals undergoing detailed assessment having been "triggered" from the targeted arm are no longer randomised and thus liable to selection bias. These individuals no longer form a representative sample. See appendix 1 for a diagrammatic representation of the MRC trial structure.

The health aspects of the detailed screening questionnaire were extensive, covering many areas. These included physical health, such as the Rose angina questionnaire(77) and mental health, with a 30 point mini mental state examination (MMSE)(78). As well as questions there were physical measures taken, including body mass index and other anthropometric data, pulse rate and blood pressure. The social status of individuals was assessed with various estimates of socio-economic status and social isolation. Current drug history was collected, which included the name, dose, frequency and potential interactions of all medications(79). Blood tests for haematology, urea and electrolytes were performed. Routine urine dipstick analysis was also performed. The detailed questionnaire can be seen in its entirety in appendix 2. The questions relating to physical health contained 15 questions specifically regarding diabetes. It was these 15 questions which formed the basis for much of this thesis. They are shown on page 15 of appendix 2, questions 38a to 38m.

Due to its size, the range of the information collected and the nature of the outcome variables (admission to hospital and death) the MRC trial of the assessment and management of older people in the community provided an extensive resource for studying diabetes in the older person.

In 2004 the full results of the original trial were published(80).

2.1.2 MRC GP Research Framework

The MRC general practice research framework (MRC GPRF) is a resource used for medical research throughout the UK. It was first established in the early 1970s and subsequently expanded throughout the 1980s. The cross section of general practices now represents the full spectrum of different practices seen throughout the UK; urban and rural locations, large and small practice size, poor and affluent locations. It now consists of over 1000 practices representing approximately 10% of the UK population. Practices who form part of the GPRF are invited to participate in trials conducted by the MRC and choose which they would like to participate in. The MRC trial for the assessment and management of elderly people in the community took place in practises belonging to the GPRF.

2.1.3 Outcome measures used in the MRC trial.

The primary outcome measures used in the MRC trial were admission to hospital, admission to institutions (hospitals, residential homes or nursing homes), quality of life and death. Quality of life data was collected on a sub sample of the trial population. The quality of life data was collected via interview prior to the detailed assessment, at 18 months and again at 36 months. This data formed the basis of the PhD undertaken by Dr Elizabeth Breeze at the London School of Hygiene and Tropical Medicine (LSHTM), the results of which are presented elsewhere(81;82). Quality of life was not considered further in this thesis.

Admission to hospital was collected for each trial participant for the two years immediately after they had completed the brief assessment. Nurses based within each participating general practice carried out six monthly notes searches on admission to hospital, based on the hospital discharge letter. The information recorded included speciality, date of admission, date of discharge and diagnosis. The hospital discharge summary has been established as a reliable method of recording discharge information(83-85).

Mortality follow up was collected for all participants in the trial. This was done by registering all trial participants with the Office of National Statistics in Southport, UK. Whenever any trial participant died and the death certificate arrived in Southport (where every death certificate in the U.K. is recorded) the details would be collected. Cause of death for all mentioned causes, including the underlying cause, was coded by ONS initially using ICD 9 and ICD 10 from October 2002. The results in this thesis were based on deaths collected until October 2003.

2.1.4 The Egton Medical Information System (EMIS)

The majority of general practitioners in the UK use clinical software to record clinical events and prescriptions. Of those who do use clinical software over 55% use software known as the Egton Medical Information System or more commonly EMIS. It was developed by two general practitioners in Egton, UK during the 1980s. The system forms an electronic record of each patient event and forms the basis of the patients medical record, held by the general practitioner. Practices in the MRC study gave their consent for their EMIS records to be accessed. EMIS data relating to the participants in the MRC trial has been collated at Nottingham University, UK. The EMIS data has been collated from the time that the general practice began using EMIS software and for the entire follow up period of each individual who participated in the original trial. EMIS data is still being updated by participating general practices for those individuals who are still alive. For approximately half of the participants in the MRC study further information regarding their health was available from the EMIS system. The EMIS data is not available for all the trial participants because not all the GP practices who were involved in the MRC trial use the system and three practices who did use it did not agree to its use in the MRC trial.

The EMIS data had two major functions; firstly it provided another method of identification of individuals with diabetes who were not identified from the detailed questionnaire and secondly as a validation tool. The EMIS data, where available, forms a representative sample of MRC trial participants. It was used to provide a sensitivity estimate for people who self reported as having clinically diagnosed diabetes. EMIS entries relating to diabetes or the use of any diabetic medication before recruitment into the MRC trial indicated that person had diabetes when they entered the MRC trial. All these people should have responded positively to the questions regarding diabetes when they completed the detailed questionnaire. Comparing the numbers of people who did actually respond positively to having diabetes in the trial questionnaire enabled a sensitivity and specificity estimate to be calculated for the question "Have you ever been told by a doctor that you have sugar diabetes?" which was used to identify trial participants with diabetes (see Chapter 3.6.8 and appendix 2).

2.2 Plan of analysis

2.2.1 Cluster randomisation

The MRC study was a cluster-randomised trial with a 2 x 2 factorial design i.e. practices were randomised to the universal arm then randomised to GM or PC or they were randomised to the targeted arm then randomised to GM or PC (see appendix 1).

When healthcare interventions are conducted at a level higher than the individual, such as organisations, regions, towns or schools, they are often randomised at the group level rather than the individual level; this is known as cluster randomisation. For example, whole schools may be allocated to intervention A and compared with schools allocated to intervention B. The MRC trial was implemented at the level of the general practice and therefore was a cluster randomised trial. There are a number of reasons why trials are conducted using cluster randomisation(86). The reasons for using cluster randomisation listed below were all applicable to the MRC study, they included;

- Public health programmes, such as the evaluation of a screening program, are generally implemented at the organisational level (in the MRC study the general practice) rather than the individual level, so cluster level randomisation was more appropriate for the evaluation of the program.

- It is potentially both unethical and/or unpractical to randomise individuals within an organisation to different treatments. It may therefore be preferable to allocate all individuals within an organisation to the same treatment.

- If individuals are randomised to different treatments within an organisation then an intervention may be susceptible to contamination bias. For example, different health promotional messages within an organisation may be communicated between individuals making true comparisons of the different interventions more difficult.

- There are practical advantages in terms of cost and time when interventions are allocated at a cluster level. Staff within each cluster have to familiarise themselves with and conduct only one intervention rather than two or more. Likewise central administration is simpler if each cluster has one intervention.

While the reasons above make cluster randomised trials seem attractive there are important statistical considerations which must be taken into account during design and analysis of a cluster randomised trial(87). When a study is conducted at the cluster level, individuals may be more highly correlated within the cluster than with individuals within other clusters. The reasons for this are listed below and were all applicable to the MRC study;

- Participants in a study have chosen the organisation to which they belong and therefore may have certain things in common. For example the general practitioner to which they are all registered.
- Cluster level attributes may have a common influence over all the individuals within that cluster. For example, outcomes of an intervention may vary systematically between practice nurses, with outcomes for patients interviewed by one practice nurse being more similar to those interviewed by another practice nurse.
- Individuals may interact within each cluster, leading to similarities between individuals within each cluster.

This lack of independence affects the statistical analysis in two ways. Firstly, there can be a marked drop in power of the study. Secondly, if observations are correlated, standard errors generated may be underestimated unless clustering has been taken into account.

To allow for the correlation between subjects, the sample size can be calculated by multiplying the formula for individually randomised trials by a quantity known as the design effect or variance inflation figure(88). The design effect can be calculated form the formula:

$$\text{Design Effect}=1+(n0-1)\rho$$

Where n0 is the average number of individuals within each cluster and ρ is the intraclass correlation coefficient. The intraclass correlation coefficient is the proportion of the total variation between the subjects within the same cluster attributable to the clustered sampling. The design effect for different outcomes was taken into account when calculating the number of clusters required for the MRC trial.

To allow for the underestimation of the standard errors which are generated consideration needs to be taken at the time of analysis. If this is not done, any confidence intervals generated from the standard errors will be too narrow and p values too small. By incorporating the design effect into conventional standard error formulas used for hypothesis testing and estimating confidence intervals, the correlation between individuals in each cluster can be taken into account(89). All the statistical analysis conducted in the following chapters were performed to allow for this. Cluster randomisation also has implications when dealing with confounding. Regression methods for dealing with confounding need to be performed at the cluster level rather than the individual level. Random effects models (multilevel models) can take into account associations between individuals within clusters. These models control for both individual level and cluster level characteristics(89).

In the MRC trial all the randomisation occurred at the general practice level by a computer generated randomisation. To ensure that the general practices did not differ in population characteristics, between randomisation groups, randomisation was stratified by Jarman Score and Standard Mortality Ratio (SMR). Practices had list sizes of between 200 and 700 patients. The sample size calculations were conducted using methods developed for use in cluster randomised trials(90). Each general practice contained a large enough sample size to conduct the MRC trial.

2.2.2 Missing data and outlying values

Categorical values were tabulated to identify missing values. To minimise the decrease in power by loss of partial information, variables with over 100 missing values had a separate missing value generated which was used in the analysis. When a variable had less than 100 missing values, the missing values were ignored and the participants with missing data excluded from that part of the analysis. The justification for this was that the dataset was of sufficient size to enable exclusion of small numbers of variables to be of little affect on the final results.

Continuous variables were visualised graphically to assess their distribution and outlying values were inspected to check their accuracy. Variables were discarded and treated as missing when they were found to be obviously wrong. For example, the date of diagnosis of diabetes stated as 1868 or diastolic blood pressure recorded as 15 mmHg.

2.2.3 Statistical software

All the analysis was conducted using Stata statistical software(91). The importance of cluster randomisation has been discussed above and this was accounted for when using Stata. The “svy” family of commands was used which were designed for multi-stage survey based clustered samples. This allowed for clustering within practices and generated the intracluster correlation coefficient.

2.2.4 Approaches to the analysis

Chapters 3 and 4 are primarily descriptive and associations were calculated using univariate analysis. Using survey commands in Stata the prevalence of diabetes was calculated and univariate analysis used to identify associations with diabetic end points and the use of diabetic services. More complex analysis in these chapters that required controlling for explanatory factors was conducted using logistic regression. The population attributable risk fraction for each diabetic endpoint was calculated using Stata. Chapter 5 concentrated on the relationships between blood pressure and diabetes. Initially diabetic end points were tested for associations with blood pressure. Blood pressure was grouped and logistic regression used. In chapter 6 the relationship between diabetes and renal function was assessed using proteinuria and creatinine measurements. These were treated as binary variables and logistic regression analysis was performed. Admission rates were assessed in chapter 7 using Poisson regression comparing the rates of admissions between all diabetic individuals and non diabetic individuals. The Poisson regression was undertaken stratifying by five year age groups. The Poisson model was tested at the 5% significance level using likelihood-ratio testing after any addition to the model of potential confounding factors or interaction terms. Chapter 8 concentrated on all cause and cause specific mortality. The cause specific mortalities were circulatory and renal mortality. All survival analyses used Cox regression analysis. Step wise Cox proportional hazard models were constructed. Potential confounding factors and interaction terms were included in the model and tested with the addition of each term to the model. After each addition to the model the proportional hazards assumption was tested to ensure it was still maintained. All variables that were left in the final model affected the hazard ratio generated by more then five percent and were significant for the Schoenfield residual test statistic at the 5% significance level. The Cox proportional hazard model was visually inspected to ensure that proportionality was maintained.

2.2.5 Potential confounding factors

Variables that were considered, *a priori*, as potential confounders were age, sex, socio-economic status measured using the Carstairs index, smoking history, alcohol intake, mini mental test score (MMSE), previous myocardial infarction, previous cerebrovascular disease, Body Mass Index (BMI) and Waist-Hip ratio (WHR).

Age, sex, socio-economic class, smoking and alcohol are common confounders. Therefore these variables should be included as potential confounding factors in any analysis where that information is available. Age was grouped using five yearly intervals, up to the age of 90, when anyone aged above this was grouped together. The Carstairs index is a measure of social deprivation(92;93). The Carstairs index is based on four component variables; overcrowding, male unemployment, social class and car ownership. The Carstairs index was obtained from postcode linkage of study participants addresses obtained from the 1991 census data. The Carstairs index was divided into quintiles, with the lowest quintile representing the poorest section of this population. Smoking, was grouped into never smokers, ex-smokers and current smokers, it did not assess pack years. Alcohol usage was classified according to the current recommendations of the Department of Health(94). It was classified into men and women who drank less and those who drank more than upper limit currently suggested. This was 21 units/week for men and 14 units for women. In 1997, the Rochester study showed that the risk of dementia is increased for both men and women with type 2 diabetes. Work conducted in the UK showed that older people with type 2 diabetes had an excess of cognitive dysfunction, associated with poorer ability in diabetes self-care and greater dependency(95). This study used a Mini Mental State Examination (MMSE) score of 23 or below for a threshold of cognitive impairment and therefore 23 was also used in this analysis. The MMSE was designed in 1975 by Folstein and collegues(78). It is a widely used and validated as a screening tool for cognitive impairment. However it is limited by the educational and language ability of participants. In addition 23 is a cut off point, someone with a score above this level may still have cognitive impairment but this would not be detected using this measure. Both previous history of myocardial infarction and cerebrovascular accident were available. They were both assessed as potential confounding factors because they indicate specific disease and comorbidity. The Nurses Health Study found that Body Mass Index (BMI) was the strongest predictor for the development of diabetes(96) and it was therefore used in this analysis. It was divided into four groups, according to the WHO guidelines(97). The classifications were; below 18.5 Kg/M^2 underweight, 18.5-25 Kg/M^2 normal weight, 25-30 Kg/M^2 overweight and over 30 Kg/M^2 obese. Epidemiological evidence also links waist-hip ratio with the development of diabetes(98). The World Health Organisation report on the definition of diabetes defines an increased waist hip ratios to be >0.90 for males and >0.85 for females(99). These figures were used in this thesis.

Further variables which were available from the MRC trial and considered for analysis were; a fall within the last six months, taking more than five medications, living alone, difficulty making ends meet, anyone to call for help and poor self rated health. The justification for using these variables is that they represent general markers of health and social isolation, which could all potentially bias the results generated. For example, if someone is taking over five medications, they are likely to have a least a modest degree of underlying pathology. Likewise if someone has no one to call for help, then they must be socially isolated to some extent.

The final four variables which were chosen *a priori* as potential confounding factors were blood pressure, systolic and diastolic, proteinuria and raised creatinine. Each of these factors are well established in the development of diabetic complications(31;33) and therefore warranted inclusion and testing in any statistical model for which diabetes was an exposure.

2.2.6 Effect modification

The prevalence of diabetes changes with age and this was supported by the findings in this study (see chapter 3) therefore it was important to consider age as an effect modifier.

Similarly the prevalence of diabetes is higher in men, again supported by this study (see chapter 3) and therefore sex was treated as a potential effect modifier when the analyses were performed.

Chapter 3. Identification of older people with diabetes and the prevalence of diabetic complications

3.1 Summary of objectives

To describe a large community based sample of older people, with and without diabetes;

To assess the prevalence of diabetes and its complications in the older person.

3.2 Background

3.2.1 Prevalence estimates of diabetes

There are numerous prevalence estimates of diabetes in the older person. Prevalence estimates, both diagnosed and undiagnosed, vary widely and are affected by a number of factors. These include age, ethnicity, the type of population studied (community, hospital or institution) and differences in the method of diagnoses(41;100-104). The prevalence generally increases with age but stabilises or even decreases in the very elderly(7;8;105-111). A Canadian community based prevalence study is one of the best examples; the study demonstrated that the prevalence of diabetes decreased from 10.2% in people aged 65-74 years to 7.8% in people aged over 85 years(111). Some examples of the differences in prevalence estimates which were available can be seen in table 3.1.

Age (years)	Reference	Year of Study	Location	No. of participants	Method of diagnosis	Prevalence of diabetes (%)*		
						Male	Female	Male and female
55	110	1995	Finland	780	Oral glucose tolerance test	10.6	6.7	(-)
60 plus	138	1989	Oxford	8520	Local cross sectional survey	(-)	(-)	3
65 plus	104	1993	Coventry	1600 (Caucasian)	Local cross sectional survey	7.7	12.5	(-)
65 plus				288 (South Asian)	Local cross sectional survey	30.7	24	
65 plus	112	2004	Europe	270306	General practice records	13.4	17.7	(-)
70 plus	111	1994	Finland	379	Oral glucose tolerance test	22	28.2	(-)
65-74	9	1987	United States	15357	50% Oral glucose tolerance test 50% nurse led questionnaire	(-)	(-)	17.7
25-49	8	2002	England and Wales	1 200 000	General practice research database	1.1	0.8	(-)
50-74						5.7	4.2	(-)
75 plus						8.5	6.4	(-)
65-85	109	1991	Melton Mowbray	861	Oral glucose tolerance test	(-)	(-)	9.3
65-74	113	1998	Canada	9008	National cross sectional survey	(-)	(-)	10.2
75-84						(-)	(-)	9.8
85 plus						(-)	(-)	7.8
65-69	107	1986	Finland	44**	Oral glucose tolerance test	13.4	(-)	(-)
70-74				35**		13	(-)	(-)
75-79				41**		13.4	(-)	(-)
80-84				13**		14.1	(-)	(-)
80 plus	108	1985	Finland	2713	Medical records	3	8.5	(-)

Table 3.1. Prevalence estimates for diabetes (arranged by age of participants)
*Includes both diagnosed and undiagnosed diabetes, **represent numbers in each age group

3.2.2 Estimations of the prevalence of microvascular complications among people with diabetes

In the older diabetic adult the amount of information that is available regarding the prevalence of microvascular diabetic endpoints is sparse. Much of the available information has been generated from small scale local studies. There are also two large scale studies which assessed several diabetic end points. The first of these was a survey of the prevalence of diabetes complications conducted in South Glamorgan, Wales(112). This study identified 10709 people with type 1 and type 2 diabetes of all ages, including people aged over 75 years. Diabetic people were identified from both GP and hospital records. The study identified several diabetic complications; retinopathy, nephropathy, coronary and cerebrovascular disease. The second large study was carried out in France and published in 2000. The French study identified 5548 patients with type 2 diabetes and assessed several micro and macrovascular end points(113). The French study population had a mean age of 63 years and were identified from electronic data records from a representative sample of French GPs. The French study considered the duration of diabetes and found that each complication increased in prevalence with increasing duration of diabetes. The prevalence of each diabetic end point derived from both these studies will be highlighted in the following paragraphs where they are appropriate in conjunction with the other available data.

The Welsh study identified retinopathy or cataract and found that over 20% of diabetic people aged over 75 years had either of these complications(112). The French study found retinopathy to increase from 7.5% in people who had suffered from diabetes for under five years to 30.0% in people who had diabetes for over 15 years, in people aged over 75 years(113). A study from Ireland, involving 150 people, newly diagnosed with diabetes, showed a prevalence of 14% for retinopathy, in patients over the aged of 70 years(114). The Wisconsin epidemiological study of diabetic retinopathy showed an overall prevalence of 39% in 151 patients aged over 70 years(115). A Welsh case control study found the prevalence of visual impairment to be 40% in older people with diabetes compared to 31% in non diabetic people(116). In Italy, the prevalence of retinopathy was found to be 24.6% in diabetic people aged over 70 years old(117) and Nathan and colleagues found similar prevalence levels of 25% in 185 diabetic people aged between 55 and 75 years(118). The duration of diabetes, the use of insulin, chronically elevated blood sugar levels and raised blood pressure have all been associated with the presence of diabetic retinopathy(114;115;117-119). Previous work done by Dr Jenny Evans at the London School of Hygiene and Tropical Medicine, on the causes of visual impairment in the elderly used the MRC trial(120;121). Using a subset of 1742 people identified with visual impairment, a hospital ophthalmologist detected diabetes as the underlying cause of visual impairment in 3.4% of cases.

The Welsh study found nephropathy to be under 5% in people aged over 75 years(112). The French study found either proteinuria or raised creatinine (>150 μmol/l) in 23.1% of diabetic people aged over 75 years with a history of having diabetes for over 15 years(113). In 821 patients aged between 50 and 75 years proteinuria was found in 29.2% of a diabetic population in South East London(122). In the same study 12.5% of the population had a creatinine level greater than 120 µmol/l(122). In 2004, the DAI study (Diabetes and Informatics study group, Italian Association of Diabetologists, and Italian National Institute of Health) found the prevalence of microabluminuria to be 25.0% in men and 19.3% in women. Proteinuria was found to be 9.5% in men and 6.1% in women. This was a large study which recruited 19468 participants. The average age in the study was 65 years for men and 67 years for women(123).

3.2.3 Estimations of the prevalence of macrovascular complications among people with diabetes

Macrovascular disease is associated with a triad of large vessel conditions; coronary artery disease, cerebrovascular disease and peripheral vascular disease.

The Welsh study from South Glamorgan estimated all forms of coronary heart disease to be over 35% in diabetic people aged over 75 years(112). The French study found "coronary insufficiency" in 20.3% of over 75 year old diabetic people. This figure rose to 36.5% in people who had had the disease for over 15 years(113). In the DAI study mentioned above (n=19468) the prevalence of coronary artery disease was 11.0% and all acute myocardial events 5.8%(123). In a population of 832 people admitted with a myocardial infarction, the prevalence of diabetes was found to be 9.7%, which was higher than an age matched group (6.1%)(124). A similar more recent study in 2050 people aged over 65 years found the prevalence of diabetes to be 28% of all myocardial admissions(125). The Minnesota Heart Survey found the prevalence of diabetes in people with myocardial infarction to be increasing since 1970 and to be greater in women than men, 25.8% vs 16.8%(126). The Framingham study found that diabetic men were more likely to have a fatal myocardial infarction and women four times more likely to develop heart failure after a myocardial infarction(127). The UKPDS 23 highlighted poor gylcaemic control, poor lipid profile, raised systolic blood pressure and a history of smoking as risk factors for the development of coronary artery disease(27). The UKPDS 66 showed that myocardial infarctions were more likely to be fatal in people with higher glucose levels, increased age, increased blood pressure and albuminuria(128).

For cerebrovascular disease, the Minnesota Heart Survey also estimated the prevalence of diabetes in people hospitalised for stroke. It was found to be 10.5% in men and 25.9% in women(129). Increased age, smoking, increased systolic blood pressure and the presence of atrial fibrillation have all been shown by UKPDS 60 to predict the risk of a first stroke(130). The largest study to date in the older person was that conducted by Barzilay and colleagues in the Cardiovascular Heart Study(131). This recruited 5712 people all aged over 65 years. They were screened for cardiac and cerebrovascular disease using several parameters. Each participant then underwent fasting glucose measurements. In people found to have known diabetes the prevalence of history of angina, myocardial infarction or cerebrovascular disease were 30.7%, 25.2% and 12.6% for men and 31.8%, 19.6% and 12.7% for women respectively. In each case the prevalence estimates were lower for those with newly diagnosed diabetes. In Wales, the South Glamorgan study identified cerebrovascular disease in approximately 20% of the population aged over 75 years(112).

When considering peripheral vascular disease, the prevalence increases with the duration of disease and was found to be 12.5% after 18 years in the UKPDS(132). Hyperglycaemia, hypertension, dyslipidemia and smoking were identified as risk factors for developing peripheral vascular disease in the UKPDS 59(132). Peripheral vascular disease itself contributes to mortality(133;134) and lower limb amputation(135) in younger diabetic populations. The majority of problems caused by peripheral vascular disease occur in the lower limb and often manifests clinically with foot problems. The World Health Organisation define the diabetic foot as a group of syndromes in which neuropathy, ischaemia and infection lead to tissue breakdown with subsequent morbidity, including amputation. Estimates suggest that about 5% of diabetic patients have a foot ulcers, these studies included a large number of older people(136-138). Over 50% of foot ulcers are due solely or in part to peripheral vascular disease(138;139). Risk factors for foot ulceration in people with diabetes of all ages include age, smoking, peripheral vascular disease, peripheral neuropathy, duration of diabetes, any injury, operation or trauma to the foot and renal disease(136;138;140;141).

3.2.4 Estimation of the prevalence of diabetic neuropathies

Diabetes may affect the central nervous system, the peripheral nervous system or the autonomic nervous system. There are no universally agreed definitions. They are usually defined based upon abnormalities detected at clinical examination. There are many different clinical manifestations, such as cranial nerve lesions, motor nerve lesions or sensory neuropathies. Neuropathies may present with or without pain and can manifest as reduced reflexes. Peripheral neuropathy was estimated in a large Italian study and found to be 32.3% in patients with an average age of 56 years(142). A smaller study in Rochester USA estimated some degree of neuropathy in up to 59% of people with type 2 diabetes(143). In an older population in Manchester UK the prevalence of neuropathy increased with age and the duration of diabetes In the participants aged between 70 and 79 years the prevalence of neuropathy was 44.2%(144).

The MRC study did not specifically assess or examine diabetic neuropathy. Therefore any estimates of the prevalence of these conditions were not possible. Diabetic neuropathy is not considered further in this thesis but their description was included for completeness.

3.3 Methods; Classification of trial participants with diabetes

3.3.1 The World Health Organisation and the American Diabetes Association classification of diabetes

In the late 1970s the National Diabetes Group(145) of the USA and the World Health Organisation (WHO)(146) produced reports which established new classification systems for diabetes. Apart from a small revision in 1985, by the World Health Organisation(147), these definitions remained unchanged for 12 years. By this time more data and aetiological information were available. Consequently in 1997 the American Diabetes Association (ADA) produced a report(3) to discuss the definition of diabetes. At the same time the WHO also convened a similar report; the conclusions of which were published in 1998(2) with the final report published in 1999(99). The ADA recommended diagnosing diabetes based on a fasting glucose above 7 mmol/l. The WHO criteria was based on a glucose level greater than 11.1 mmol/l measured two hours after an oral glucose load of 75g. However there was much agreement between the reports. Both reports reduced the threshold level of glucose needed to be diagnosed as having diabetes. The aim of both was to maximise accurate and early diagnoses in an attempt to prevent morbidity and mortality. Nonetheless identification of people with diabetes may vary according to which criteria is used(18;103;148). For example, a famous study known as the DECODE study compared 13 populations in eight European populations(149). They concluded that using fasting glucose caused an increase in prevalence by 0.8%. Further work from the DECODE group suggested that abnormal fasting glucose levels are more often seen in middle aged obese patients while thinner elderly people are more likely to have abnormal glucose levels after an oral glucose load(103).

For epidemiological purposes the WHO recommends the use of the blood glucose measurements two hours after an oral glucose load but states that fasting glucose alone is also a satisfactory measure(99).

3.3.2 Criteria used for the identification of diabetic individuals within the MRC trial of older people in the community

Thorough identification of participants in the MRC trial with diabetes was essential to ensure the results and conclusions generated were accurate. All participants in the trial identified with diabetes were used throughout the subsequent analysis.

To correctly identify all the trial participants with diabetes, using the universal questionnaire, they were identified according to their self reporting response, high random glucose and whether they were receiving diabetic medication. The EMIS database was then searched for any further trial participants diagnosed as having diabetes. Trial participants will ultimately be divided into those with diabetes (cases) and those without diabetes (non cases). Participants with diabetes (cases) were based on the self reporting of diabetes using the detailed questionnaire in the MRC trial, high random glucose, the use of diabetic medications and participants with diabetes identified from the EMIS database.

All questionnaires with a positive response to the question “Have you ever been told by a doctor that you have sugar diabetes?” were examined, to ensure that the responder really did have diabetes.

Using random glucose measurements (fasting glucose was only recorded in five individuals in the MRC trial) further trial participants were identified as having diabetes. These glucose measurements were not taken two hours after a 75g oral glucose load. Although this does not satisfy the WHO(99) or ADA(3) criteria for the classification of diabetes (see section 3.1.1 above) it is likely that many of these people will have diabetes. A cut of point off 11.1 mmol/l was used in the MRC study. The rational being that a random glucose of 11.1 mmol/l or above in the presence of symptoms of diabetes is another criteria used for the diagnosis of diabetes(99). Unfortunately, while the MRC study collected large amounts of information, the specific presence of diabetic symptoms were not collated.

The third method for the identification of diabetic individuals, from the universal questionnaire, was to find the trial participants who were receiving diabetic medication. In this age group diabetic drugs; insulin and oral hypoglycaemic drugs, are used exclusively in diabetic individuals. Anyone found to be taking these medications had diabetes.

Finally the EMIS database was searched for diabetic terms to find any remaining trial participants who had been diagnosed with diabetes before they were entered into the trial.

Failure to identify and treat individuals as having diabetes has several implications. It would have underestimated the true level of both diagnosed and undiagnosed diabetes in the community. It would have also impacted on the survival analysis of the diabetic participants, leading to an underestimation of the affect of diabetes, as not all diabetic participants would have been included in the analysis. This is nondifferential (random) misclassification. The affect of this type of misclassification is to increase the similarity between the group with diabetes and the group without diabetes thus diluting or underestimating any associations. Any results obtained would have been biased towards the null value.

3.4 Methods; Classification and identification of the complications of diabetes

3.4.1 Microvascular complications

Diabetic Retinopathy (Visual Impairment)

Diabetic retinopathy is assessed using retinal visualisation. This can be done using direct fundoscopy, retinal photography or fluorescein angiography. These techniques detect well defined retinal disease caused by diabetes. However, none of these procedures were done in the MRC trial. Therefore, in order to detect diabetic retinal disease in the study population a proxy measured had to be used; visual acuity. The epidemiological consequences of using visual impairment as a proxy measure for diabetic retinopathy is considered in the discussion section of this chapter (section 3.9).

To test visual acuity all participants who underwent the detailed questionnaire in the universal arm of the MRC study had their visual acuity measured at 3 metres with a Glasgow acuity chart. This measured the minimal angle of resolution on a logarithmic scale (logMAR). Binocular vision was measured, followed by vision in either eye separately, using any spectacle correction. Trial participants with a logMAR visual acuity more than 0.5 or more in either eye were retested with a pinhole occluder. A logMAR visual acuity of more than 0.5 is equivalent to less than 6/18 Snellen acuity. The International Classification of Diseases 10th Edition (ICD 10) defines low vision as a visual acuity less than 6/18 but equal or better than 3/60. It defines blindness as visual acuity less than 3/60 in the better eye. The term visual impairment was used in this thesis to mean both low vision and blindness. Visual impairment is presented for trial participants with diabetes.

Diabetic Nephropathy

Diabetic nephropathy is a term used to describe abnormal renal function in people with diabetes. The MRC trial collected two measures which were useful in assessing the renal function of the diabetic population. These were proteinuria and raised creatinine levels. Both of these factors represent proxy measures for diabetic nephropathy.

Diabetic nephropathy typically presents with proteinuria followed by rising blood creatinine levels as renal function worsens. Typically diabetic nephropathy begins with the loss of protein into the urine. The amount of protein lost into the urine tends to increase. Diabetic nephropathy is diagnosed (and defined) when more than 300 mg of protein is lost into the urine in a 24 hour period. All trial participants had a sample of urine tested for the presence of protein (yes or no). The exact diagnosis of diabetic nephropathy requires two samples to be positive for protein within one year. In addition, samples may be positive for protein in the absence of diabetic renal disease e.g. in the presence of urinary infection. A blood sample was obtained during the detailed questionnaire, which was tested for creatinine (μmol/l). Typically 120μmol/l creatinine is used an upper limit of normal for renal function. Any level above 120 μmol/l was therefore used as a cut off point to determine any associations with diabetes and poor renal function.

Creatinine measurements alone, while useful, are prone to variation between individuals. Several factors can lead to abnormal creatinine levels; kidney disease itself, reduced muscle mass (commonly seen in older people), ingestion of cooked meat, malnutrition and the use of certain medications (cimetidine and trimethoprim being examples). Consequently, since the 1950s, another measure of kidney function has been regarded as the gold standard of estimation of renal function; the Glomerular Filtration Rate (GFR)(150). GFR is estimated from the urinary clearance of an ideal filtration marker (a filtration marker is a substance freely filtered by the kidney, without secretion or reabsorbtion) and is defined by:

$$Ci = UiV/Pi$$

where Ci is the clearance of the ideal filtration marker (i), Ui is the urinary concentration of i, V is the urine flow rate, and Pi is the average plasma concentration of i during the time interval of urine collection. In clinical practice the precise measurement of GFR is difficult to achieve. It requires urine collection and the administration of filtration markers. Therefore extensive attempts have been made to estimate the GFR directly from creatinine levels, such as the commonly used Cockcroft and Gault formula(151). In 1999, Levey and colleagues developed several estimating equations for GFR based on creatinine levels(152). These equations were adopted (in modified form) in 2002 by the National Kidney Foundation in America and are now widely established and form an accurate measure of GFR, surpassing previously used estimating equations(153;154). The data on which the estimating equations was based was the Modification of Diet in Renal Disease Study and the equation is known as the abbreviated MDRD study equation. The formula is:

$$\text{GFR (ml/min per 1.73 m}^2\text{)} = 186 \times (\text{SCr})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female})$$

SCr is serum creatinine concentration (mg/dL), age in years. There is another correction factor for people of black origin (not shown here). The detailed questionnaire did not obtain information regarding ethnicity and therefore this additional correction factor was not used when calculating GFR. In 2005, the MDRD study equation was evaluated in two studies involving diabetic people and found to be more accurate than the Cockcroft-Gault formula(155;156). The first study used 160 people with diabetes, 50 had type1 and 110 type 2 diabetes. The age ranged between 19 and 83 years with a mean age of 62.2 years(155). The second trial used the large cohort (n=1286) of diabetic people from the DCCT, therefore this population was exclusively comprised of type 1 diabetic individuals(156). Both studies noted imperfections with the MDRD equation but considered it to be more accurate at calculating GFR when compared to the Cockcroft-Gault formula. It was therefore the MDRD equation that was used to calculate GFR for diabetic participants in the MRC study.

The 2002 guidelines from the National Kidney Foundation(153) have highlighted two levels of GFR. The first was 60 ml/min per 1.73 m^2. GFR measurements below this level represent the loss of at least half the normal adult level of normal kidney function(154). The second level was a GFR less than 15 ml/min per 1.73 m^2, which in most cases will be accompanied by symptoms of uraemia. In the United States 98% of patients need to start renal replacement therapy when their GFR falls below this level(154). In the UK renal function is graded into five stages. GFR below 60 ml/min per 1.73 m^2 corresponds to stage 3 (moderate) disease and less than 15 ml/min per 1.73 m^2 corresponds to stage 5 (established renal failure). The distribution of the GFR is presented here for the diabetic population.

3.4.2 Macrovascular complications

Coronary Heart Disease

Coronary heart disease can present in a number of ways. These include angina (typically pain on exertion which is relieved with rest), myocardial infarction or sudden death. The WHO (Rose) chest pain questionnaire is a well validated and long standing method of defining and identifying angina and severe coronary ischemia for use in epidemiological studies(157;158). Questionnaire responses accurately predict death due to coronary heart disease(77). In 1998 Lampe and colleagues used a simplified version of the questionnaire to identify angina(159). They suggested that the use of three questions alone can be used to identify angina in epidemiological studies. A missing response for one or more questions precludes a diagnosis of angina. The three questions used to identify angina were all included as part of the MRC trial and are shown in appendix 2, (questions 9(a), 9(b) and 9(c)). The questions were:

- Have you ever had any pain in your chest?
- Do you get this pain or discomfort when you walk uphill or hurry?
- Do you ever get it when you walk at an ordinary pace on the level?

The same paper also suggested that recall of a doctor diagnosis of ischaemic heart disease is a very strong predictor for the presence of severe ischaemic heart disease(159). Therefore the question "Have you ever been told that you have had a heart attack?" was assessed to determine the prevalence of previous myocardial infarction in participants in the MRC trial. Therefore prevalence of angina and myocardial infarction are presented for trial participants with diabetes.

Cerebrovascular Disease

A diagnosis of cerebrovascular disease is usually a clinical one. Investigations such as computerised tomography of the brain are useful but not essential when making a diagnosis of stroke. The use of such imaging has only become routine in the past few years following initiatives such as the National Service Framework for Older People(37). Recruitment for the MRC study finished in 1997 and it is likely that many of participants who had a stroke would not have undergone imagining. Therefore it is likely that responses to the question "Have you ever been told that you have had a stroke?" (yes or no) accurately represented the prevalence of cerebrovascular disease within the diabetic population. The results for this question in trial participants with diabetes are given below.

Peripheral Vascular Disease

Peripheral vascular disease is a condition which affects the large blood vessels of the peripheral circulation, most typically the lower limb. It can result in pain, ulceration or amputation. Pain may be constant or associated with walking and relieved by rest, when it is known as intermittent claudication. The UKPDS 59 identified peripheral vascular disease if two of three of the following criteria were identified in either leg; 1. ankle-arm blood pressure index (ratio) <0.8, 2. neither dorsalis pedis or posterior tibial pulses were palpable (these are pulses which should normally be felt in the foot and ankle) or 3. intermittent claudication was reported. The MRC study collected data on the presence of foot or leg ulcers, whether they were being treated and if they were healing (see appendix 2 questions 47(a), 47(b) and 47(c)). The questions were:

- Have you ever had any leg or foot ulcers?
- If yes, are they/is it being treated?
- Are they/is it healing alright?

The types and aetiology of foot ulceration are numerous and are not solely caused by peripheral vascular disease or diabetes. The MRC questionnaire regarding foot ulceration did not distinguish between different types of ulcer. Neither did it collect information regarding intermittent claudication, ankle-arm blood pressure indexes, peripheral pulses or amputation. Therefore the presence of foot ulcers in people with diabetes are presented. If ulceration was present whether they were being treated and whether they were healing is also shown.

Please note that occasionally the numbers involved in each sub group analysis were small. Where less than five individuals were present in each group the calculation of prevalence estimates became inaccurate. This was because the standard errors generated were very large. Consequently where this occurs the number of participants was given in the results tables without a prevalence estimate.

3.5 Results; Description of the participants who underwent detailed assessment in the MRC trial of older people in the community

The full description of the MRC trial of the assessment and management of older people can be found in the methods section (Section 2.1.1).

The following factors were used to describe the population.

- Number of participants
- Age
- Sex
- Additional descriptive factors, including those which were considered as potential confounders, are provided to give a fuller picture of the population. The factors assessed were the Carstairs index, living alone, reporting no one to call for help if required and reporting often or always having difficultly making ends meet. Measures of general health status were assessed by reporting one or more falls at home within the last six months, taking five or more medications and self reporting of a participants own health as either poor or fair.
- Smoking, alcohol, mini-mental state examination (MMSE), previous myocardial infarction, previous cerebrovascular disease, body mass index (BMI) and waist hip ratio (WHR).

3.5.1 Description of the universal arm of the MRC trial

The dataset comprised 21410 individuals aged 75 and over, who were eligible and invited to participate in the universal arm of the MRC trial. A total of 15095 (70.5%) of 21410 people randomised to the universal arm, completed the full assessment.

The mean age was 81.30 years, with the median age 80.38 years. The age range was from 75.01 years to 108.04 years. The inter-quartile range was 77.23 years to 101.31 years.

There were 5776 (38.26%) males and 9319 (61.74%) females. The women were older ($p<0.001$) with a median age of 80.98, the median age of the male trial participants was 79.76.

Age group	Male(%)	Female(%)	Total(%)
75-79 years	3014 (52.2)	4028 (43.2)	7042 (46.7)
80-84 years	1746 (30.2)	3012 (32.3)	4758 (31.5)
85-89 years	820 (14.2)	1621 (17.4)	2441 (16.2)
90 plus years	196 (3.4)	658 (7.1)	854 (5.6)
Total	5776 (100)	9319 (100)	15095(100)

Table 3.2. Age and sex distribution of participants who underwent detailed assessment

The were 13846 participants who had sufficient information recorded to enable the Carstairs index to be completed. Participants in the lowest (most deprived) quintile were more likely to be male ($p<0.001$) and older ($p<0.001$). Those in the youngest age groups and men were more likely to be heavy drinkers, ex and current smokers, have the highest BMI and an increased hip waist ratio ($p<0.001$ for all). Women and those at increased age were most likely to have a MMSE=<23 ($p<0.001$). There was no missing data for alcohol or MMSE, 1992 participants had missing smoking data, 1250 participants had missing body mass index, 314 men and 680 had missing waist hip ratio measurements. There were no differences between people with and people without missing data in terms of age and sex. The results for Carstairs index, MMSE, alcohol, smoking, body mass index and waist hip ratio are all given in table 3.3.

Variable		Whole Population n=15095 (%)	Men n=5776 (%)	Women n=9319 (%)
Carstairs by quintile	1st (least deprived)	3264 (21.62)	1336 (23.13)	1928 (20.69)
	2nd	3688 (24.43)	1454 (25.17)	2234 (23.97)
	3rd	3161 (20.94)	1181 (20.45)	1980 (21.25)
	4th	2268 (15.02)	856 (14.82)	1412 (15.15)
	5th (most deprived)	1465 (9.71)	506 (8.76)	959 (10.29)
	missing	1249 (8.27)	443 (7.67)	806 (8.65)
MMSE	<=23	3156 (20.91)	947 (16.40)	2209 (23.70)
	>23	11939 (79.09)	4829 (83.60)	7110 (76.30)
	missing	0	0	0
Alcohol	0-21 units	(-)	5585 (96.69)	(-)
	>21 units	(-)	191 (3.31)	(-)
	0-14 units	(-)	(-)	9177 (98.48)
	>14units	(-)	(-)	142 (1.52)
	missing	(-)	0	0
Smoking	Never	5117 (33.90)	968 (16.76)	4149 (44.52)
	Ex-smoker	6694 (44.35)	3500 (60.60)	3194 (34.27)
	Current	1292 (8.56)	633 (10.96)	659 (7.07)
	missing	1992 (13.20)	675 (11.69)	1317 (14.13)
BMI	<18Kg/m2	261 (1.73)	58 (1.00)	203 (2.18)
	18-25	5643 (37.38)	2119 (36.69)	3524 (37.82)
	25-30	5616 (37.20)	2450 (42.42)	3166 (33.97)
	>30	2325 (15.40)	753 (13.04)	1572 (16.87)
	missing	1250 (8.28)	396 (6.86)	854 (9.16)
WHR	<0.90 (men)	(-)	1418 (24.55)	(-)
	>0.90 (men)	(-)	4044 (70.01)	(-)
	<0.85 (women)	(-)	(-)	4901 (52.59)
	>0.85 (women)	(-)	(-)	3738 (40.11)
	missing	(-)	314 (5.44)	680 (7.30)

Table 3.3. Characteristics of the whole population

There were 7081 (46.91%) individuals in the universal arm who lived alone and a total of 288 (1.91%) participants stated that they had no one to call for help. There were 423 (3.03%) participants who had difficulty making ends meet and there were 3144 (20.82%) participants who had at least one fall at home in the last six months. In all, 3307 (21.91%) participants were taking more than five medications and 2418 (16.18%) participants rated their own health as fair or worse.

3.5.2 Description of the non responders

Of the 21410 participants who were randomised to the universal arm of the trial. There were 6315 (29.5%) who did not complete the assessment. This group includes a small number (169) of people who were found to be ineligible, for example, aged under 75 at recruitment. It also includes a larger group who underwent the brief assessment but failed to complete the universal assessment. This group of non completers totalled 1601 (7.48%). For the purposes of this thesis anyone who failed to complete the full assessment, for whatever reason, will be termed a non responder. Age and sex were the only descriptive factors available for non responding participants. Men were more likely to respond than women (80.5% vs 76.7%, $p<0.001$), and this sex difference persisted after adjustment for age: the adjusted odds ratio for response comparing men with women was 1.22 (95% CI 1.16-1.29, $p<0.001$). Responders were slightly younger than non responders (median 80.3 years vs 81.0 years, $p<0.001$). All non-responders were followed up for mortality. The mortality rates for the non responders are presented in chapter 8.

3.6 Results; identification of individuals with diabetes

Trial participants were identified who potentially had type 2 diabetes (see section 3.3.1-6 below). After the identification of any person who may have had diabetes their original trial questionnaire was examined. Every questionnaire was examined at least once. The results are summarised in table 3.4 and figure 3.1 below.

3.6.1 Identification of trial participants with type 1 diabetes

The year of diagnosis of diabetes was used to identify any trial participant who may have had type 1 diabetes. Chapter 1 described the poor life expectancy for anybody diagnosed with type 1 diabetes mellitus in the early part of this century, even after the advent of insulin therapy in 1922(40). There were 18 trial participants identified as having diabetes who recoded their date of diagnosis as 1922 or before. Life expectancy before the advent of insulin therapy was only 2.6 years, therefore it is extremely unlikely that this response is correct. All these people were assumed to have type 2 diabetes mellitus. In trial participants identified as having diabetes, who recorded a year of diagnosis, their age at diagnosis implied that they had type 2 diabetes i.e. they were all aged at least 40 years old. There were 197 participants with diabetes who had not recorded a year of diagnosis. None of these people was taking insulin alone which is prerequisite for a diagnosis of type 1 diabetes. Similarly these people were assumed to have type 2 diabetes. Ultimately there was no one in the universal arm of the MRC trial who was considered to have type 1 diabetes.

3.6.2 Missing responses for diabetes mellitus

There were 53 participants who had a missing response to the question “Have you ever been told by a doctor that you have sugar diabetes?”. All of these questionnaires were examined. More women (33) had missing data than the men (p=0.006). Individuals with missing data were more likely to be older ($p<0.001$) than those without.

Of the 53 questionnaires there were 49 questionnaires with no evidence of diabetes (no further questions relating to diabetes mellitus were completed, all of them had a normal random glucose, none of these participants were receiving diabetic medication and for those with EMIS records, none had any record of having diabetes). For all future analysis in this thesis these individuals were classified as not having diabetes.

There was one person with a missing entry for diabetes who subsequently responded correctly to all the further questions relating to diabetes (appendix 2, page 15). In addition they had a random glucose greater than 11.1mmol/l. This participant was classified as responding positively to having diabetes (true positive response) and was treated as having diabetes for future analysis.

There was one entry who had a random glucose greater than 11.1 mmol/l and had a missing response for diabetes. They had not answered any further questions relating to diabetes and they were not taking any diabetic medication. This person was treated as having high random glucose for the future statistical analysis

There was one entry with a missing response for diabetes who had a random glucose greater than 11.1 mmol/l and was taking diabetic medication, although they had not answered any further questions relating to diabetes. This person was classified as responding negatively to having diabetes mellitus (false negative response), but for the analysis was treated as having diabetes.

There was one participant with a missing response for diabetes who had responded to a few, but not all of the other questions relating to diabetes mellitus (see appendix 2, page 15). This person did not have a high random glucose and they were not taking any diabetic medication. This person was classified as having responded negatively to having diabetes mellitus and was treated as not having diabetes mellitus for future statistical analysis.

3.6.3 Self reporting of diabetes mellitus

There were 992 individuals who responded positively to the question "Have you ever been told by a doctor that you had sugar diabetes?". After inspection of each questionnaire, only three of these had no evidence to support the diagnosis of diabetes. All three had not responded positively to any of the further questions relating to diabetes (see appendix 2, page 15). None of these individuals were taking diabetic medication and none of them had a random glucose greater than 11.1 mmol/l. These three entries were recoded as not having diabetes for all subsequent analysis. These three individuals were false positive responders. There was one individual who was reclassified as responding to this positively to this question who originally had a missing response (see section 3.6.2 above). Therefore the total number of people identified from this question was 990 (see table 3.4).

3.6.4 High random glucose

There were a total of 129 individuals who had responded negatively to the question regarding a diagnosis of diabetes and one missing responder (see section 3.6.2 above) who had a random glucose greater than 11.1 mmol/l and were not taking diabetic medication.

None of them had responded positively to the further questions relating to diabetes (see appendix 2). All of these people were unaware of having diabetes and formed the basis of the prevalence estimate of undiagnosed diabetes in the community (see section 3.6.7 below).

All 130 individuals with a high random glucose were recoded as having diabetes (cases) for the purposes of future statistical analysis for the majority of this thesis. The exception being chapter 4. This chapter considered the understanding of diabetes and the use of diabetic services and individuals with a high random glucose were not considered as cases. This was because these people had not been diagnosed with diabetes and therefore would not have been in a position to receive diabetic education or to have been offered the opportunity to utilise diabetic services.

3.6.5 The use of diabetic medication

There were 15 individuals who had responded negatively when asked about a diagnosis of diabetes but who were receiving diabetic medication. All 15 were considered as false negative responders. For the statistical analysis in this thesis they were recoded as having diabetes (cases).

3.6.6 Participants with diabetes identified from the EMIS data

There were a total of 6273 (41.56%) who entered the universal arm who had EMIS data available. A total of 42 people were further identified as having diabetes from the EMIS data. The EMIS database was searched for participants who were receiving diabetic medication or who had a diagnosis of diabetes before they were entered into the MRC trial. All these individuals were considered as false negative responders. They were reclassified as having diabetes (cases) for the remainder of the thesis.

3.6.7 Overall estimates for the prevalence of diabetes mellitus

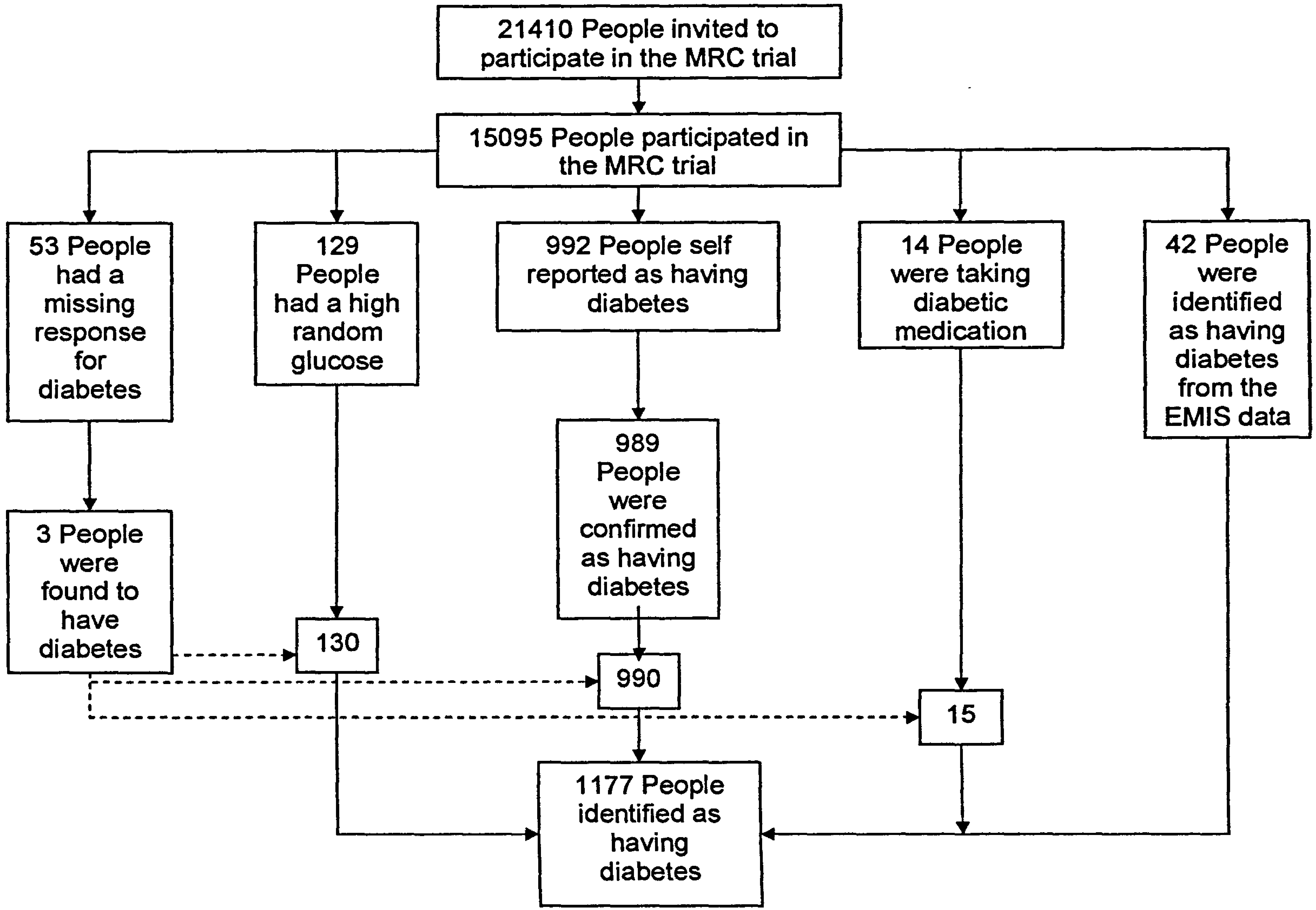
The total number of trial participants who were identified as having type 2 diabetes mellitus was 1177 out of 15095 who underwent detailed assessment. The prevalence of diabetes in men and women aged over 75 years was 7.80% (95%CI 7.11-8.47). The results are shown in table 3.4 below. For the future statistical analysis these will be the cases and any trial participant without diabetes mellitus will now be considered as a non case.

The majority (990) of participants with type 2 diabetes mellitus were identified directly from the screening questionnaire, 130 were identified due to a high random glucose and 15 because they were receiving drugs for diabetes. A further 42 participants with diabetes were identified from the EMIS data The prevalence of undiagnosed diabetes in the community is therefore 0.86% (95%CI 0.96-1.02) (130 individuals with high random glucose divided by the total study population 15095).

Different trial participants identified as having diabetes mellitus	Number (proportion)
Identified from the questionnaire	990 (84.11)
Identified from high random glucose	130 (11.05)
Identified from drug data	15 (1.27)
Identified from EMIS data	42 (3.57)
Total	1177 (100)

Table 3.4 Breakdown of the source of the participants identified as having diabetes mellitus.

Figure 3.1 Flow diagram demonstrating the identification of diabetic participants



3.6.8 Sensitivity estimates for response to questions relating to diabetes mellitus.

The responses of the trial participants were assessed. This allowed an estimation of the accuracy of the response to the question "Have you ever been told by a doctor that you have sugar diabetes?" to be tested. The responses to this question for each person identified as having diabetes were divided into the four groups shown below:

1. Those who self reported as having diabetes and had evidence of having diabetes (true self report positive individuals).

2. Those who self reported as having diabetes but who had no evidence of having diabetes (false self report positive individuals).

3. Those who self reported as not having diabetes but who had evidence of having diabetes (false self report negative individuals). This group did not include individuals with a high random glucose. This was because these people were unaware of their condition and could not have been expected to report positively that they had the disease.

4. Those trial participants who self reported as not having diabetes and who had no evidence of having diabetes (true self report negative).

The EMIS data was used to provide sensitivity and specificity estimates for people who self reported as having diabetes. EMIS entries relating to diabetes or the use of any diabetic medication before recruitment into the MRC trial indicated that person had diabetes. All these people should have responded positively to having diabetes mellitus. Comparing the numbers of people who did actually respond positively provided the sensitivity and specificity estimates.

EMIS data was available for 6273 individuals who entered the universal arm of the trial. Of the 990 participants who responded positively when asked if they had diabetes 360 had EMIS data available.

A sensitivity estimate was calculated for self reporting in detecting previously diagnosed diabetes. This figure was calculated from the 360 positive responders to the question "Have you ever been told by a doctor that you have sugar diabetes?", who had EMIS data available and 47 individuals who responded negatively to that question but were found to have diabetes (42 from the EMIS data alone and 5 people who were receiving diabetic drugs and had EMIS data available). The sensitivity estimate was therefore calculated to be 88.5%, (313/360).

A specificity estimate was calculated for self reporting in detecting previously diagnosed diabetes. The specificity estimate was calculated from all the trial responders who appropriately said that they did not have diabetes and the three responders who said they diabetes when they actually had no evidence that they did have diabetes (all three had EMIS data available). The specificity estimate was calculated to be 99.9% (5863/5866).

Table 3.5 shows the results, note that the numbers represent only those participants for whom EMIS data was available.

	Evidence of diagnosed diabetes		Total
"Have you ever been told that you have sugar diabetes?	Yes	No	
Yes	360	3	363
No	47	5863	5910
Total	407	5866	6273

Table 3.5. Responses to the screening question for diabetes.

3.6.9 Individuals with glycosuria

There was another group of participants within the MRC trial who warranted discussion. These were the trial participants who had glycosuria only without any other evidence of having diabetes. Glycosuria may be associated with renal glycosuria, a benign condition, tubular disorders such as Fanconi syndrome, cystinosis, Wilson disease, hereditary tyrosinemia, or oculocerebrorenal syndrome (Lowe syndrome). In a population aged over 75 years the presence of glycosuria may well reflect undiagnosed diabetes. However, glycosuria in isolation is not diagnostic of the condition and these people could not be classified as having diabetes with any certainty. There were 129 people with glycosuria. Glycosuria was not considered further in this thesis.

3.6.10 Duration of diabetes

It would have been useful to have known the length of time each diabetic participant had been suffering from the disease. Duration of disease is an unmodifiable risk factor, which correlates with the occurrence of diabetic end points. Unfortunately it was not possible to calculate accurately the duration of disease. Firstly, there were 197 participants with diabetes who had not recorded a year of diagnosis. Secondly, and more importantly, the date of diagnosis of the diabetic end point was not recorded. Therefore it was virtually impossible to correlate the duration of diabetes with the onset of diabetic end points.

3.7 Results; Description of the individuals defined as having diabetes mellitus

The participants identified in the trial as having diabetes were then described using the same factors as the participants in the universal arm of the trial (see section 3.5).

The mean age of participants with diabetes was 80.94 years, with a median value of 80.02 years, which was slightly younger than people without diabetes who's mean age was 81.33, with a median value of 80.41 years, ($p=0.007$). There were more women with diabetes 633 (53.78%) than men 544 (46.22%) $p<0.001$ (table 3.6). The prevalence of diabetes in men was 9.42% (8.44-10.50) and in women 6.79% (6.10-7.56) $p<0.001$. The age specific prevalence of diabetes was higher in men compared to women for people aged 75-79 years only ($p<0.001$).

Age group	Male(%)	Male Age Specific Prevalence (%) (95% CI)	Female(%)	Female Age Specific Prevalence (%) (95% CI)	Total(%)	Age Specific Prevalence* (%) (95% CI)
75-79 years	309 (56.80)	10.25 (9.14-11.46)	276 (43.60)	6.85 (6.01-7.69)	585 (49.70)	8.31 (7.56-8.49)
80-84 years	151 (27.76)	8.64 (7.14-10.14)	213 (33.65)	7.07 (6.14-8.00)	364 (30.93)	7.65 (6.89-8.49)
85-89 years	67 (12.32)	8.17 (6.10-10.24)	100 (15.80)	6.17 (4.69-7.65)	167 (14.19)	6.84 (5.60-8.33)
90 plus years	17 (3.13)	8.67 (4.82-12.52)	44 (6.95)	6.69 (4.79-8.59)	61 (5.18)	7.14 (5.61-9.05)
All ages	544 (100)	9.42 (8.44-10.50)	633 (100)	6.79 (6.10-7.56)	1177 (100)	7.80 (7.11-8.47)

Table 3.6 Age and sex prevalence of trial participants with diabetes

*men and women

The were 1087 (out of 1177) participants with diabetes mellitus who had sufficient information for the Carstairs index to be completed. The 90 diabetic people without Carstairs data available were missing either all or part of the information required to complete the Carstairs index. Like the main trial participants, those in the lowest quintile (indicating the greatest social isolation) were more likely to be male ($p<0.001$) and older ($p<0.001$). The odds ratio for MMSE less than 23 was 1.33 (1.14-1.55) for participants with diabetes compared to those without diabetes. Both men and women with diabetes were less likely to drink above the recommended weekly amounts, odd ratios 0.57 (0.35-0.97) and 0.71 (0.51-0.98) respectively. There were 430 (36.53%) participants who had diabetes and had never smoked. Participants with diabetes were more likely to be ex-smokers or current smokers than those without diabetes (test for trend $p<0.001$). Body Mass Index (BMI) greater than 30Kg/M^2 was more common 278 (23.62%) in those with diabetes than those without diabetes ($p<0.001$). Increasing BMI was also related to diabetes (test for trend $p<0.001$). Both men and women with diabetes had an increased odds ratio of having a waist hip ratio above 0.90 ($p=0.04$) and above 0.85 ($p<0.001$) respectively. These results are shown in table 3.7.

	Variable	Non diabetic Population n=13918 (%)	Diabetic Popualtion n=1177 (%)	Odds ratio* (95% CI)	P value
Carstairs by quintile	1st (least deprived)	3063 (22.01)	201 (17.08)	1	(-)
	2nd	3398 (24.41)	290 (24.64)	1.31 (1.12-1.51)	<0.001
	3rd	2889 (20.76)	272 (23.11)	1.45 (1.21-1.73)	<0.001
	4th	2055 (14.77)	213 (18.10)	1.59 (1.24-2.04)	<0.001
	5th (most deprived)	1354 (9.73)	111 (9.43)	1.28 (0.99-1.65)	0.06
	missing	1159 (8.33)	90 (7.65)	(-)	(-)
MMSE	<23	2874 (20.65)	282 (23.96)	1	(-)
	>23	11044 (79.35)	895 (76.04)	1.33 (1.14-1.55)	<0.001
	missing	0	0	(-)	(-)
Alcohol	0-21 units (men)	5049 (96.50)	536 (98.89)	1	(-)
	>21 units (men)	183 (4.50)	8 (1.11)	0.57 (0.35-0.97)	0.04
	0-14 units (women)	8546 (98.38)	631(99.68)	1	(-)
	>14units (women)	140 (1.62)	2 (0.32)	0.71 (0.51-0.98)	0.04
	missing	0	0	(-)	(-)
Smoking	Never	4754 (35.16)	363 (30.84)	1	(-)
	Ex-smoker	6098 (43.81)	596 (50.64)	1.12 (0.95-1.32)	0.18
	Current	1212 (8.71)	80 (6.80)	0.76 (0.58-0.99)	0.04
	missing	1854 (13.31)	138 (11.72)	(-)	(-)
BMI	<18Kg/m2	348 (2.50)	15 (1.27)	1	(-)
	18-25	5205 (37.40)	336 (28.55)	1.41 (0.75-2.67)	0.28
	25-30	5182 (37.23)	434 (36.87)	1.78 (0.96-3.33)	0.07
	>30	2047 (14.71)	278 (23.62)	3.03 (1.61-5.68)	<0.001
	missing	1136 (8.16)	114 (9.69)	(-)	(-)
WHR	<0.90 (men)	1306 (24.96)	112 (20.59)	1	(-)
	>0.90 (men)	3654 (69.84)	390 (71.69)	1.24 (1.01-1.54)	0.04
	missing	272 (5.20)	42 (7.72)	(-)	(-)
	<0.85 (women)	4648 (53.51)	253 (39.97)	1	(-)
	>0.85 (women)	3405 (39.20)	333 (52.61)	1.80 (1.52-2.12)	<0.001
	missing	633 (7.29)	47 (7.42)	(-)	(-)

Table 3.7. Characteristics and odds ratios for diabetic and non-diabetic populations
*adjusted for age and sex

There were 508 (43.16%) individuals who lived alone who were identified as having diabetes. Those with diabetes were less likely to live on their own than those without diabetes (p=0.007). A total of 18 (1.53%) participants with diabetes had no one to call for help but no more than those without diabetes (p=0.58). There were 44 (3.74%) participants with diabetes who had difficulty making ends meet, no more than those without diabetes (p=0.14). There were 300 (25.49%) participants with diabetes who had at least one fall at home in the last six months which was more than those without diabetes ($p<0.001$). A total of 402 (34.15%) participants with diabetes were taking at least five medications, this was more than participants without diabetes ($p<0.001$) and 254 (21.58%) participants with diabetes rated their own health as fair or worse, again more than those without diabetes ($p<0.001$).

3.8 Results; The complications of diabetes mellitus

3.8.1 Microvascular complications

Diabetic eye disease

Eye disease was grouped into those with low vision (Snellen<6/18) or blindness (Snellen<3/60), as described in section 3.4.1 above. There were a total of 523 (3.46%) individuals who completed the detailed questionnaire but had no visual acuity measure recorded for low vision or blindness. People with missing entries for low vision were more likely to be female ($p<0.001$), older ($p<0.001$) and have diabetes ($p=0.02$). For all participants, those with low vision or blindness were more likely to be female ($p<0.001$) and older ($p<0.001$). Diabetic people had a higher prevalence of visual impairment and blindness when compared to the non diabetic population: 12.66% (95%CI 12.62-12.70) vs 9.80% (95%CI 9.79-9.81) ($p<0.001$) for visual impairment and 3.01% (95%CI 2.91-3.11) vs 2.04% (95%CI 2.03-2.05) ($p<0.001$) for blindness. For the diabetic participants sex did not affect the presence of low vision or blindness. In diabetic people low vision ($p<0.001$) and blindness ($p<0.001$) were all associated with increasing age. The amount of low vision and blindness attributable to diabetes (assuming complete causation), measured using the population attributable risk fraction (PAF), was 3.46% and 1.02% respectively.

The full results can be seen in tables 3.8 and 3.9. Crude, adjusted odds ratios and PAF for low vision and blindness attributable to diabetes can be seen in table 3.12.

		Number	Visual Impairment (<6/18) % (95% CI)	Number	Blindness (<3/60) % (95% CI)
All participants		1480	10.15 (8.97-11.33)	308	2.11 (1.80-2.42)
Missing		*523*		(-)	
	Men	327	7.07 (6.07-8.07)	96	1.71 (1.34-2.08)
	Women	1083	12.09 (10.64-13.54)	212	2.37 (1.92-2.82)
75-79 years	Men	104	3.52 (2.71-4.33)	20	0.68 (0.38-0.98)
	Women	217	5.53 (4.45-6.61)	27	0.69 (0.34-1.04)
80-84years	Men	133	7.86 (6.64-9.08)	38	2.24 (1.46-3.02)
	Women	300	10.34 (8.62-12.06)	68	2.34 (1.70-2.98)
85-89 years	Men	115	14.71 (11.80-17.69)	26	3.32 (2.19-4.45)
	Women	346	22.54 (19.47-25.61)	76	4.95 (3.79-6.11)
90 plus years	Men	45	24.86 (18.24-25.48)	12	6.63 (3.20-10.06)
	Women	220	36.97 (32.32-41.62)	41	6.89 (4.74-8.03)

Table 3.8. Prevalence of visual impairment and blindness with age and sex distribution of all participants

		Number	Visual Impairment (<6/18) % (95% CI)	Number	Blindness (<3/60) % (95% CI)
Diabetic participants		149	13.27 (12.00-14.54)	35	3.12 (2.14-4.10)
Missing		*54*		(-)	
	Men	62	11.85 (10.43-12.27)	13	2.49 (1.20-3.78)
	Women	87	14.5 (13.0-16.0)	22	3.67 (2.05-5.29)
75-79 years	Men	28	9.36 (6.05-12.67)	5	1.67 (0.30-3.04)
	Women	25	9.51 (6.08-12.94)	4	1.52 (0.15-2.89)
80-84years	Men	22	14.86 (9.55-20.17)	7	4.72 (1.69-7.78)
	Women	18	8.82 (4.96-12.68)	9	4.41 (1.53-7.29)
85-89 years	Men	9	15.00 (5.85-24.15)	1	(-)
	Women	28	30.10 (22.07-38.14)	6	6.45 (1.44-11.47)
90 plus years	Men	3	(-)	3	(-)
	Women	16	40.00 (26.56-53.44)	0	(-)

Table 3.9 Prevalence of visual impairment and blindness with age and sex distribution of diabetic participants.

Diabetic renal disease

Proteinuria was recorded as the presence of *at least* one plus of protein on a urinary dipstick testing (yes or no). There were a total of 995 out of 15095 (6.59%) people who had a missing record for proteinuria. The response was more likely to be missing in women ($p<0.001$) and with increasing age group ($p<0.001$). However, diabetic participants were just as likely to have missing data compared to people without diabetes ($p=0.77$). For the 1177 participants who were identified as having diabetes there were 1097 (93.20%) participants who had a response. Diabetic participants with missing data were more likely to be older ($p=0.004$) than diabetic participants without missing data, although there was no difference in the number of missing responses between men and women with diabetes.

There were a total of 1581/15095 (10.47%) non diabetic people who had proteinuria. Proteinuria was found in 188/1177 (17.14%) of the diabetic participants, which was more than those without diabetes ($p<0.001$). For all participants, women were more likely to have proteinuria ($p=0.002$) and participants were older ($p<0.001$). Diabetic participants with proteinuria were not more likely to be older or of different sex.

Raised creatinine was defined as serum creatinine above 120µmol/l. There were 1942/15095 (12.87%) participants who had no creatinine measurement recorded. Participants without a creatinine measurement were both older and more likely to be women ($p<0.001$). For the diabetic participants 135/1177 (11.47%) had a missing creatinine which was not more than those without diabetes.

The diabetic participants with missing creatinine more likely to be women ($p=0.008$) but not older.

There were 2404/15095 (18.28%) people with a creatinine greater than 120µmol/l. they were more likely to be men and older ($p<0.001$). There were 236/1177 (22.65%) diabetic participants with raised creatinine. Diabetic participants were more likely to have raised creatinine ($p<0.001$) than non diabetic participants. Diabetic participants with raised creatinine were more likely to be women ($p<0.001$) and older ($p=0.002$).

The PAF for proteinuria attributable to diabetes was 6.99% and for raised creatinine the PAF attributable to diabetes was 5.35%.

The results can be seen in table 3.10 and 3.11. Crude and adjusted odds ratios for proteinuria, raised creatinine and PAF are given in table 3.12.

The glomerular filtration rate (GFR) was calculated for the participants in the trial. As creatinine was used to calculate this value there were the same number of missing values for GFR as for creatinine (1942/15095, 12.87%). For the trial participants without diabetes the mean GFR was 58.30 ml/min per $1.73m^2$ (95%C.I. 58.04-58.57). This was not significantly higher than participants with diabetes, whose mean GFR was 58.09 (95%C.I. 57.09-59.08), ($p=0.65$). For comparison the average creatinine measurements were compared in the diabetic and non diabetic populations. Creatinine was significantly higher in the diabetic population; 105.19 (95%CI 103.29-107.10) vs 101.36 (100.79-101.92), $p=0.007$.

Likewise, no differences were detected when GFR was assessed using the established cut off points of 60 and 15 ml/min per $1.73m^2$. People with diabetes were no more likely to be in either of these groups than people without diabetes, ($p=0.89$ and $p=0.86$, respectively). Visual inspection of the distributions of GFR for people with and people without diabetes showed both to be normally distributed and not skewed.

		Number	Proteinuria % (95% CI)	Number	Raised creatinine % (95% CI)
All participants		1581	11.21 (8.72-13.7)	2404	18.28 (16.87-19.69)
Missing		*995*		*1942*	
	Men	669	12.23 (9.93-14.43)	1444	28.23 (25.78-30.68)
	Women	912	10.57 (8.27-12.87)	960	11.94 (10.73-13.15)
75-79 years	Men	315	10.98 (8.64-13.32)	630	23.38 (20.33-26.43)
	Women	350	9.21 (6.70-11.72)	268	7.53 (6.26-8.90)
80-84years	Men	216	13.01 (9.27-16.73)	473	30.54 (27.66-33.48)
	Women	280	10.07 (7.28-12.88)	354	13.64 (11.78-15.50)
85-89 years	Men	114	14.81 (10.57-19.06)	267	38.03 (34.49-41.57)
	Women	203	13.77 (9.89-17.65)	220	16.02 (14.22-17.82)
90 plus years	Men	24	14.04 (8.78-19.30)	74	43.53 (36.18-50.88)
	Women	79	13.76 (9.75-17.77)	118	22.91 (18.72-27.10)

Table 3.10 Prevalence of proteinuria and raised creatinine with age and sex distribution of all participants

		Number	Proteinuria % (95% CI)	Number	Raised creatinine % (95% CI)
Diabetic participants		188	17.14 (13.26-21.00)	236	22.65 (19.79-25.49)
Missing		*80*		*135*	
	Men	89	17.32 (12.73-21.91)	151	30.44 (25.74-35.14)
	Women	99	16.98 (12.24-21.72)	85	15.57 (11.77-19.37)
75-79 years	Men	53	18.21 (12.78-23.64)	73	25.89 (19.30-32.48)
	Women	42	15.97 (10.80-21.14)	24	9.87 (6.19-13.55)
80-84years	Men	25	17.12 (8.16-26.08)	45	33.09 (25.43-40.75)
	Women	33	16.92 (10.16-23.68)	34	18.47 (12.30-24.64)
85-89 years	Men	9	14.51 (4.67-24.35)	29	47.54 (36.92-58.16)
	Women	20	22.47 (11.92-33.01)	19	22.61 (13.02-32.19)
90 plus years	Men	2	(-)	4	(-)
	Women	4	(-)	8	22.85 (8.46-37.42)

Table 3.11 Prevalence of proteinuria and raised creatinine with age and sex distribution of diabetic participants

	Crude odds ratio (95%CI)	Odds ratio* (95%CI)	P value (fully adjusted* Wald test)	PAF%
All participants	1	1	(-)	(-)
Diabetic participants				
Vision <6/18	1.39 (1.17-1.65)	1.59 (1.32-1.90)	<0.001	3.46
Vision <3/60	1.55 (1.09-2.22)	1.72 (1.19-2.47)	0.004	1.02
Proteinuria	1.72 (1.42-2.09)	1.72 (1.42-2.09)	<0.001	6.99
Creatinine >120µmol/l	1.34 (1.16-1.55)	1.25 (1.07-1.46)	<0.001	5.35

Table 3.12 Crude and adjusted odds ratios and PAF for diabetic participants and microvascular complications

*adjusted for age, sex and smoking

3.8.2 Macrovascular complications

Cardiovascular disease

The presence of angina was evaluated using the questions outlined in section 3.4.2. It used three questions relating to chest pain to establish a diagnosis of angina as proposed by Lampe *et al*(159). For a diagnosis, an answer needed to be present for each of the three questions. The first question was simply "have you ever had pain or discomfort in your chest?" It required a yes or no answer. A person answering no was not required to answer the following two questions. The vast majority of the respondents 13480 out of 15095 (89.30%) answered no. Only 49/15095 (0.29%) people had a missing response for this question, this small number of missing responses (less than 100) will not be considered further. There were 1566/15095 (10.41%) people who responded to all three questions relating to angina. Of the 1566 people with angina, they were more likely to have diabetes, be female and be younger ($p<0.001$, for each). Considering the people with diabetes and angina, they were no differences between sex or age. The results are shown in tables 3.13 and 3.14.

History of a previous myocardial infarction was ascertained from the detailed questionnaire. There were 138/15095 (0.91%) people with a missing response for a previous history of myocardial infarction. Those with a missing response to this question were not older, different sex or more likely to have diabetes than those without a missing response.

There were 1603/15095 (10.62%) people who had had a myocardial infarction and 190/1177 (16.14%) people with diabetes who had had a myocardial infarction. People with diabetes were more likely to have had a myocardial infarction than those without diabetes ($p<0.001$). Women were more likely to have had a myocardial infarction than men ($p=0.001$) and participants were more likely to be older ($p<0.001$). Of the diabetic people, those who had had a myocardial infarction were not more likely to be older or of different sex than diabetic people who had not had a myocardial infarction. The PAF for angina attributable to diabetes (assuming complete causality) was 3.31% and 4.82% for myocardial infarction. The results are shown in tables 3.13 and 3.14.

Cerebrovascular disease

A previous diagnosis of cerebrovascular disease was determined from the questionnaire. There were 119 out of 15095 (0.79%) people with a missing response for this question. People with a missing response to this question were not older, of different sex or more likely to have diabetes than those without a missing response. There were 1338/15095 (8.86%) people who had had a cerebrovascular accident and 163/1177 (13.94%) people with diabetes who had had a cerebrovascular accident. A cerebrovascular accident was more likely to have occurred in people with diabetes ($p<0.001$). Women were more likely to have had cerebrovascular accident than men ($p=0.006$), people who had suffered a cerebrovascular accident were also younger ($p<0.001$). In people with diabetes, those who had had a cerebrovascular accident were the same sex and not more likely to be older. The results are shown in tables 3.13 and 3.14. The PAF for CVA attributable to diabetes was 2.56%. Crude, adjusted odds ratios and PAF for angina, myocardial infarction and cerebrovascular accidents can be seen in table 3.16.

		Number	Angina % (95% CI)	Number	Myocardial Infarction % (95% CI)	Number	Cerebrovascular Accident % (95% CI)
All participants		1566	10.41 (9.49-11.32)	1603	10.62 (9.89-11.35)	1338	8.93 (8.15-8.71)
Missing		*49*		*138*		*119*	
	Men	668	11.59 (10.28-12.90)	806	14.07 (12.90-15.23)	570	9.93 (8.97-10.89)
	Women	898	9.68 (8.80-10.56)	797	8.64 (7.89-9.39)	768	8.31 (7.66-8.96)
75-79 years	Men	336	12.16 (10.69-13.63)	425	14.20 (12.85-15.55)	264	8.81 (7.69-9.93)
	Women	415	10.33 (9.11-11.55)	310	7.75 (6.91-8.59)	269	6.72 (5.72-7.72)
80-84years	Men	216	12.39 (10.39-14.39)	257	14.82 (12.98-16.66)	167	9.60 (7.95-11.25)
	Women	322	10.73 (9.55-11.91)	265	8.87 (7.69-10.05)	264	8.83 (7.81-9.85)
85-89 years	Men	74	9.04 (7.08-11.00)	102	12.56 (10.03-15.09)	117	14.39 (10.88-17.90)
	Women	128	7.93 (4.21-11.14)	168	10.53 (8.84-12.22)	161	10.08 (8.55-11.61)
90 plus years	Men	12	6.25 (3.25-9.25)	22	11.51 (7.36-15.65)	22	11.58 (7.54-15.62)
	Women	33	5.07 (3.00-8.14)	54	8.39 (6.27-10.51)	74	11.42 (8.44-15.40)

Table 3.13 Prevalence of coronary and cerebrovascular disease with age and sex distribution of all participants

		Number	Angina % (95% CI)	Number	Myocardial Infarction % (95% CI)	Number	Cerebrovascular Accident % (95% CI)
Diabetic participants		151	12.10 (10.24-13.96)	190	16.14 (14.46-18.06)	163	13.94 (11.86-16.02)
Missing		*7*		*9*		*8*	
	Men	71	13.08 (10.20-15.96)	102	18.85 (15.83-21.87)	84	15.47 (12.45-18.49)
	Women	80	12.76 (10.41-15.11)	88	14.04 (11.47-16.61)	79	12.62 (9.97-15.27)
75-79 years	Men	44	14.24 (10.65-17.83)	67	21.82 (17.21-26.43)	46	14.94 (10.22-18.66)
	Women	40	14.55 (10.81-18.29)	34	12.41 (8.25-16.56)	36	13.14 (9.08-17.22)
80-84years	Men	18	11.92 (5.67-18.17)	20	13.33 (8.31-18.35)	22	14.57 (8.53-18.61)
	Women	23	10.90 (6.08-15.72)	29	13.62 (9.41-17.83)	27	12.74 (8.78-16.70)
85-89 years	Men	7	10.61 (3.75-17.47)	11	16.41 (8.37-24.45)	14	20.90 (12.37-29.43)
	Women	11	11.22 (6.44-16.00)	18	18.75 (11.67-25.83)	14	14.58 (7.84-21.32)
90 plus years	Men	2	(-)	4	(-)	2	(-)
	Women	6	13.95 (1.70-26.20)	7	15.91 (3.56-28.26)	2	(-)

Table 3.14 Prevalence of coronary and cerebrovascular disease with age and sex distribution of the diabetic participants, (-) not stated due to insufficient cases

Peripheral vascular disease

Individuals with foot ulceration were identified from the detailed questionnaire as described above (see section 3.4.2). Those with foot ulceration were then required to answer further questions relating to treatment and healing. There were 644 out of 15095 (4.27%) missing responses to this question. People with missing responses were of similar sex, similar age and no more likely to have diabetes than those without missing responses. There were 404/15095 (2.80%) people with foot ulceration. There were 303/404 (75.00%) of this group who were receiving treatment for their foot ulcer and 280/404 (69.31%) reported that their foot ulcer was healing. People with foot ulceration were more likely to be female ($p=0.013$) and older ($p<0.001$). People with diabetes were more likely to have foot ulceration ($p=0.004$). There were 47/1177 (4.14%) people with diabetes and foot ulceration. There were 41/47 (87.23%) of this group who were receiving treatment for their foot ulcer and 37/47 (78.72%) reported that their foot ulcer was healing. The diabetic people with foot ulceration were not older or of different sex than diabetic people without foot ulceration. The PAF for foot ulceration attributable to diabetes was 1.09. The results are shown in tables 3.15 and 3.16. Crude, adjusted odds ratios and PAF for foot ulceration can be seen in table 3.16.

		All participants		Diabetic participants	
		Number	Presence of foot ulceration % (95% CI)	Number	Presence of foot ulceration % (95% CI)
Overall		404	2.80 (2.42-3.24)	47	4.14 (2.74-5.54)
Missing		*644*		*42*	
	Men	131	2.36 (1.90-4.82)	20	3.82 (2.07-5.57)
	Women	273	3.06 (2.52-3.60)	27	4.41 (2.61-6.21)
75-79 years	Men	50	1.72 (1.23-2.24)	9	3.01 (2.03-3.99)
	Women	79	2.04 (1.46-2.72)	10	3.72 (1.71-5.73)
80-84years	Men	42	2.52 (1.66-3.38)	7	4.82 (1.56-8.10)
	Women	84	2.92 (2.15-3.65)	7	3.38 (1.61-4.77)
85-89 years	Men	29	3.71 (2.31-5.11)	3	(-)
	Women	74	4.82 (3.67-5.97)	6	6.45 (1.41-11.49)
90 plus years	Men	10	5.38 (2.08-8.71)	1	(-)
	Women	36	5.71 (3.70-7.72)	4	(-)

Table 3.15 Prevalence of foot ulceration with age and sex distribution of both all and diabetic participants

	Crude odds ratio (95%CI)	Odds ratio* (95%CI)	P value (fully adjusted* Wald test)	PAF%
All participants	1	1	(-)	(-)
Diabetic participants				
Angina	1.36 (1.15-1.60)	1.32 (1.11-1.56)	<0.001	3.31
Myocardial Infarction	1.57 (1.31-1.89)	1.50 (1.24-1.83)	<0.001	4.82
Cerebro-vascular accident	1.69 (1.34-2.13)	1.97 (1.33-2.11)	<0.001	2.56
Foot ulceration	1.56 (1.10-2.23)	1.65 (1.15-2.36)	<0.001	1.09

Table 3.16 Crude and adjusted odds ratio for diabetic participants and macrovascular complications
*adjusted for age, sex and smoking

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3.9 Discussion

The results from this chapter were used primarily for the analysis in the rest of the thesis. They also provided estimates for prevalence, descriptive factors associated with diabetes and diabetic complications and these factors are discussed below.

The results from the description of the universal arm of the MRC trial show that the participants were distributed as expected for an elderly population. There were more women who were older than the men. The participants in the trial with diabetes had a similar distribution of age and sex, with more older women. The diabetic participants were also younger than the trial participants without diabetes.

In the MRC trial all participants with diabetes were assumed to have type 2 diabetes. Typically, type 1 diabetes is thought of as a disease of young people with absolute pancreatic failure occurring at presentation of the disease to medical care. In clinical practice about 10% of people of middle and older age present with a clinical picture of diabetes which is similar. They present with rapidly progressive disease which requires the use of insulin for disease control within a matter of months. Therefore one can speculate the prevalence of type 1 diabetes is around 10% in the older person. However, in the MRC trial no one was identified with any certainty as having type 1 diabetes and must therefore be treated as having type 2 diabetes mellitus.

The prevalence estimates of type 2 diabetes found from the MRC study were broadly similar to other community based estimates. Like previous studies there was a decrease (or stabilisation) of prevalence with increasing age(7;8;102;106-111;160). This study represents by far the largest community based questionnaire of the prevalence of diabetes in older people published in the world. The largest previously conducted study was conducted by Rockwood and colleagues and involved 9008 Canadian elders(161). The results, generated from the MRC trial, for the age groups 85-89 years and 90 plus years are the only estimates available anywhere for these specific age groups. Previous estimates have not agreed on whether men or women have a higher prevalence of diabetes(7;110). The results from the MRC study demonstrated a higher prevalence of diabetes in men compared to women for each age specific prevalence estimate, although only the estimate for the age range 75-79 years reached statistical significance.

However, it is likely that the estimates produced here underestimate the true figure. There are a number of factors that could have contributed to this underestimation. Firstly, it is likely that despite thorough searching of the available data sources not all of the participants with diabetes were identified because they self reported inaccurately, did not have a high random glucose at the time of the assessment and were not taking any diabetic medication. Further attempts to identify participants with diabetes were made using the EMIS database. This identified a further 42 participants with diabetes. This number was also an underestimate because EMIS data was only available for 6273 of the trial participants and therefore not all records could be checked. Despite this, questionnaires based on interviews have been used previously to identify diabetic people for use in cohort studies and are commonly used for this type of research. For example, the National Health and Nutrition Examination Study (NHANES) which was a representative cohort study of 15374 individuals aged 25-74 years identified diabetic people using a similar method to the MRC study. It recruited 725 diabetic people based on an interview only. The cohort was, and still is, followed for mortality(162). The second factor that could have contributed to the underestimation of the true prevalence of diabetes is that older people with diabetes are more unwell than those without diabetes and therefore less likely to have participated in this study. Within the MRC trial it was not possible to identify and assess these individuals. Comparison of mortality rates between the non responders and the responders for the universal arm was conducted in chapter 8 to assess this and is discussed in more detail then.

The estimation of undiagnosed diabetes (0.86%) seems very low compared to previous U.K. estimates of up to 2%. This may have been due to the lack of an OGTT. In studies that have identified diabetic people using an OGTT the prevalence of undiagnosed diabetes has been much higher(8;109).

For the whole population the quintiles of Carstairs index show that the population comes from a range of different social backgrounds. A large proportion (24.73%) of this elderly population came from the two lowest quintiles, which represent the most deprived population, with 21.62% coming from the highest. In both the population as a whole and in the participants with diabetes, men were more likely to come from the lowest quintile of the Carstairs index and those in the lowest quintile were older. These results for both all the participants and those with diabetes are consistent with published data relating to the distribution of elderly populations within the Carstairs index(92;93).

When comparing the whole population and the population with diabetes there was no difference between the groups in terms of no one to call for help and difficultly making ends meets. This implies that people with diabetes are not necessarily more socially isolated than people without diabetes. Furthermore participants with diabetes were less likely to live alone, again implying less social isolation within the diabetic population. Participants from nursing homes have been excluded from entry into the trial. Therefore people with diabetes being more likely to live in nursing homes (and therefore less likely to live alone) would not account for the finding that people with diabetes were less socially isolated. It is possible that greater social networks develop around people with diabetes. Another explanation could be that the study population is biased. It is possible that our trial population, like all participants in medical studies, have increased health awareness and are generally more healthy. Such individuals may be more likely to take steps to prevent social isolation by developing greater social networks. Unsurprisingly trial participants with diabetes were more likely to be taking at least five medications and that they rated their health as being worse than people without diabetes. There was also an increased risk of falls in those with diabetes. There are two possible medical explanations for the increased number of falls; firstly hypoglycaemia induced by diabetic medication or secondly as a result of the disease process itself e.g. increased falling associated with diabetic neuropathy. For example subgroup analysis of a large prospective study of older women with osteoporosis found that the chances of having a fall were higher in any woman who had diabetes and even higher in those diabetic women who were taking insulin(163). However the authors concluded that this was because of a generally increased prevalence of falls risk factors rather than any one specific factor.

The results for smoking were interesting. It shows that participants with diabetes were more likely to be current smokers or ex-smokers than those without diabetes. The increased number of ex-smokers could be attributable to smoking cessation advice which is heavily aimed a diabetic individuals but why there should be greater numbers in the first place is unclear. Smoking increases the risk of several long term complications of the disease but is not strongly implicated in the aetiology of the disease itself. Cross sectional studies have shown greater insulin resistance in smokers, although HbA1c levels have not been found to have been raised(164). It is possible that smoking itself may have a greater aetiological role in diabetes in the older person.

People with diabetes had lower MMSE scores than people without diabetes; odds ratio 1.33 (1.14-1.55). This result is in agreement with those obtained previously in Wales and America(95;165). The decreased MMSE reflects the increased risk of dementia, of all types, in people with diabetes(165).

It has long been established that obesity contributes to the aetiology of diabetes in the younger person and the results in this elderly population support the association between obesity and risk of diabetes. The age and sex adjusted odds ratio for having a BMI over 30 Kg/M^2 was 3.03. There was also a significant trend for increasing BMI in people with diabetes. The adjusted odds ratios for having diabetes and an increased waist hip ratio (WHR) were increased for both men and women; 1.24 (1.01-1.54) and 1.80 (1.52-2.12) respectively. These results implied that even at older age an increased WHR still predisposed an individual to having diabetes.

Unsurprisingly, in the diabetic population each of the complications assessed in this study was found to have higher prevalence than in the non diabetic population. After adjustment for age and sex, the odds ratio for each complication remained raised when comparing the two groups.

When considering the prevalence estimates overall, they seemed to be lower for each specific complication than had previously been estimated from other studies. While the differences seen may have been due to chance the generally lower prevalence estimates seen were probably due to an underestimation of the overall diabetic prevalence detected from the MRC study. An underestimation of the true figure for the prevalence of diabetes, which is discussed above, will result in bias. There will be a non random misclassification. This will result in a dilution of the effect of diabetes and hence the prevalence of diabetic complications

Specific complications and their prevalence estimates are discussed and compared in more detail to previous studies below.

The studies of diabetic eye disease have previously assessed diabetic retinopathy rather than visual impairment and above the age of 75 years few studies have been conducted. The estimates of prevalence highlighted in the introduction to this chapter (section 3.2.2) ranged between 7.5% for diabetes of five years duration to above 40%(112-117). The studies from South Glamorgan, Wisconsin and Italy all found the prevalence of retinopathy to be over 20%(112;115;117).

The prevalence of visual impairment among people with diabetes obtained from the MRC trial was 13.27%. However the MRC trial did not assess diabetic retinopathy, making direct comparisons with previous studies difficult. Retinopathy may be present without deterioration in vision. It was likely that some of the diabetic population in the MRC trial had diabetic eye disease which had not yet affected their vision. In epidemiological studies which perform fundoscopy, retinopathy may be more likely to exhibit a higher prevalence than decreased visual acuity. However, the higher prevalence of visual impairment in the diabetic group and PAF of 3.46%, indicate that diabetes does add to the burden of visual impairment. The overall prevalence of visual impairment but not blindness was slightly higher in women than men, but there was not any difference between the age and sex specific prevalence measures.

In South East London, 29.2% of their diabetic clinic population had proteinuria and 12.5% of the population had a creatinine level greater than 120 µmol/l(122). The prevalence level of proteinuria obtained from the MRC trial (17.14%) was less than this. Our estimate is higher than those obtained from the DAI study in Italy(123). This study found proteinuria to be 9.5% in men aged on average 65 years and 6.1% in women aged on average 67 years. The MRC trial population was older than both of these studies suggesting that proteinuria may increase with age. The raised PAF detected in the MRC study (PAF=7.0%) implied that diabetes contributes to the burden of proteinuria in older diabetic people. A large percentage of the older diabetic population in the MRC trial had raised creatinine 22.65%. This figure is much higher than the 5% estimate of nephropathy obtained from South Wales, for reasons for which were not clear(112). While diabetes seems to have contributed to raised creatinine (adjusted odds ratio 1.25), this was not reflected in reduced glomerular filtration rate in this age group. In fact, there was no difference in the GFR calculated for the diabetic and the non diabetic group using the Modification of Diet in Renal Disease Study (MDRD) equation(152;154). The MDRD equation has only been validated in younger diabetic populations(155). It was surprising that no differences were found between the diabetic and non diabetic groups because the creatinine levels were higher in the diabetic group. It is therefore possible that the MDRD equation becomes less reliable at the extremes of age in diabetic (and possibly all) populations. Furthermore, when the GFR was assessed by grouping, either less than 60 or less than 15 ml/min/1.73m^2, people with diabetes did not exhibit worse renal function. This may have also reflected inaccuracies in the calculation of GFR using the MDRD in the older diabetic person. Visual inspection, of the distributions of GFR, showed that both the non diabetic and the diabetic populations were normally distributed. If the distribution had not been normal, a non parametric test should be used to test any differences between the means of the diabetic and non diabetic populations. Therefore a non normal distribution, occurring after the generation of GFR using the MDRD equation, does not account for the lack of difference observed.

The MRC trial estimated the prevalence of angina among people with diabetes to be 12.10% and myocardial infarction to be 16.26%. These estimates were community based using a well validated method of recall(159). The results therefore represent slightly different estimates to some of those which were discussed in the introduction to this chapter (section 3.2.3). For example; a study in 2050 people aged over 65 years in

Connecticut, U.S. found the prevalence of diabetes to be 28% of all myocardial admissions(125), slightly lower than the 35% seen in South Wales, which included both in patients and out patients(112). The Minnesota Heart Survey estimated the prevalence of diabetes in people hospitalised for myocardial infarction. It was found to be 16.8% in men and 25.8% in women(129).

Perhaps the most comparable study to the MRC trial was the Cardiovascular Heart Study(131). This recruited 5712 people all aged over 65 years, from 4 study sites in America. Each participant then underwent fasting glucose measurements. In people found to have diabetes, the prevalence of history of angina and history of myocardial infarction were 30.6% and 25.2% for men and 31.8% and 19.6% for women respectively. The overall prevalence of angina and myocardial infarction in our diabetic population were lower than these figures and did not vary between men and women; 12.10% and 16.26% respectively. The higher prevalence seen in the Cardiovascular Heart Study may reflect a higher underlying prevalence of diabetes, detected because each participant underwent fasting glucose measurement. In the DAI study from Italy (n=19468) the prevalence of coronary artery disease was 1.1% and all acute myocardial events 5.8% in type 2 diabetic patients of all ages in a hospital outpatient setting(123). This may be a comparable survey to the MRC trial and the differing results obtained reflected the younger age of the Italian population. The increased PAF for each complication shows that diabetes contributes to the burden of macrovascular disease in older age, especially myocardial infarction.

The prevalence of cerebrovascular disease was very similar between the Cardiovascular Heart Study and the MRC trial(131). The Cardiovascular Heart Study demonstrated a prevalence of 12.6% for men and 12.7% for women. The MRC trial showed an overall prevalence of 13.94%. The sex specific prevalence was 15.47% for men and 12.62% for women. This figure is less than the 20% seen in South Wales but this study identified both in patients and out patients(112).

The prevalence of peripheral vascular disease was found to be 12.5% after 18 years in the UKPDS(132) in whose population was younger. We did not have the capacity to estimate peripheral vascular disease itself Equally, there are detailed classification systems available for foot ulcers, such as the Wagner classification. Therefore, the self reporting of foot ulceration was taken as representing, however crudely, the presence of peripheral vascular and foot disease. Over 50% of foot ulcers are due solely or in part to peripheral vascular disease(138;139). Estimates suggest that about 5% of diabetic patients have a foot ulcers (these studies included a large number of older people)(136-138). The prevalence estimate recorded in the MRC trial is slightly below that figure, 4.14%, but broadly similar.

It is likely that the prevalence estimates of diabetic complications produced by this survey underestimate the true figures because not everybody with diabetes was identified due to the reasons outlined above. This is nondifferential (random) misclassification. This increases the similarity between the group with diabetes and the group without diabetes thus diluting or underestimating any associations. Any results obtained will be biased towards the null value.

It is also likely that not all diabetic complications were detected. Physical measurements by trained study personnel were taken for visual acuity, proteinuria and creatinine, while there is always the possibility of bias, these measures probably reflect accurate reproducible results. The identification of cardiac disease, cerebrovascular disease and foot ulceration required self reporting. All self reporting is subject to recall bias, although the cardiac measures have been well validated(157-159). The others have not been so well validated and this must be noted as a limitation. Another factor contributing to the underestimation of the true prevalence of diabetic complications is that older people with diabetes and complications are more unwell than those with diabetes without complications. Diabetic people with complications are therefore less likely to have participated in this study. Within the MRC study it was not possible to identify and assess these individuals beyond comparing mortality rates between responders and non responders which was performed in chapter 8.

Chapter 4. The management of diabetes in the older person and patient understanding of their diabetes

4.1 Summary of objectives

To assess the:

Source of medical advice and treatment regimes;

Degree and type of home glucose testing;

Hypoglycaemia and individual understanding of diabetes management;

Utilisation of diabetic services;

Affect of management and understanding on diabetic endpoints.

4.2 Background

4.2.1 Introduction

Modern diabetic management is multi-disciplinary and life long. Once a diagnosis of diabetes has been established the daily management is largely patient based, with patients taking responsibility for their own care. Therefore a high degree of emphasis is given to self management by patients themselves, through diabetes education and empowering individuals.

There are several components of successful long term patient based management of diabetes. These include; diet, self-medication, monitoring blood glucose, regular medical review and the use of specialties allied to diabetes. The aim of which are to reduce morbidity and mortality from diabetes. The National Service

Framework for diabetes (NSF)(4) first published in December 2001, provided a blueprint for care, which formalises the standard of care a diabetic person can expect. Three of those standards are especially relevant to this chapter; standards 3, 4 and 10. Each of them and their subsequent recommendations concern the routine management and understanding of the condition;

Standard 3 is dedicated to empowering individuals to manage their condition themselves.

Standard 4 states "All adults with diabetes will receive high-quality care throughout their lifetime, including support to optimise the control of their blood glucose, blood pressure and other risk factors for developing the complications of diabetes".

Standard 10 states "All young people and adults with diabetes will receive regular surveillance for the long-term complications of diabetes."

Within the NSF clinical guidelines and pathways have been developed by the National Institute for Clinical Excellence (NICE) for management of diabetic retinopathy(166) and by the Royal College of General Practitioners for the management of foot care(167).

4.2.2 The diabetic annual review

An important part of the NSF is the diabetic annual review, which is the recommended minimum frequency for diabetic consultations(4). The annual review is solely centred around diabetes, rather than other health issues. It provides a point of contact for the diabetes services and an environment for the systematic review of an individuals diabetic care. A typical annual review would include blood glucose levels, blood pressure, renal function, examination of eyes and feet and any diabetic issues relevant to the consultation. The annual review may be conducted in hospital or within the primary care setting. The exact local model will vary between different hospitals and primary care trusts. Thus, the majority of people with diabetes are under the care of a medical professional; either a hospital based consultant, their general practitioner, a diabetic specialist nurse or a combination of all three. Current estimates suggest that at least half of diagnosed diabetic patients attend hospital for their diabetes(168). A study from Leeds of 100 elderly diabetic inpatients found that 19% did not receive any medical supervision for their condition(169). General Practitioners may also provide specialist clinics, if they have a particular interest in diabetes. A literature review from 1996 suggested that between 13% and 20% of general practices provide specialist diabetic care(170). The results in this chapter provide an assessment of the medical management and treatment regimes that the older diabetic person undergoes in the U.K.

4.2.3 Home glucose testing

Home glucose testing is designed to maximise a persons ability to mange their own disease; tightly regulating blood sugar while at the same time preventing hypoglycaemia. As discussed above (see section 1.1.5) chronic hyperglycaemia contributes to the long term complications of diabetes. It follows that it is important to monitor blood glucose levels, attempting to maintain blood sugar as low as possible, in relation to diet and medication, while avoiding hypoglycaemia.

Therefore many individuals, young and old, are taught how to perform home glucose testing, a common method of testing blood sugar quickly and accurately. This can be either testing of blood or urine. The testing of blood is done via a small pin prick to the finger and testing the resulting drop of blood. Hand held meters provide a measure of current blood glucose to one tenth of one mmol/l of glucose. Home glucose testing is time consuming, requires dexterity and can be painful. Urine testing detects the presence of glucose in the urine. It provides a graded estimate recording the amount of glucose in the urine (a reflection of the glucose in the blood) using an increasing series of "+"s. The minimum threshold for identification of urinary glucose is a blood glucose concentration of approximately 10mmol/l. Below this level glucose is reabsorbed in the kidney and not excreted into the urine. It does not provide as accurate a measure as blood testing and also does not record hypoglycaemia. It simply detects the presence, and to a less accurate extent, the degree of hyperglycaemia. Blood testing has now largely superceded urine testing, although urine testing is an older and simpler method. Therefore many older people, particularly if diagnosed several years ago, still test their urine.

While many diabetic people test their glucose levels at home, limited benefits in the older person have so far been identified. It has also not been established that blood glucose testing confers additional benefits to urinary glucose testing. One of the few studies to show benefit from regular blood testing was conducted in Italy, in non insulin treated type 2 diabetic people aged up to 75 years(171). In 988 patients they showed a small improvement in long term blood glucose levels in people who performed at least six blood tests per week, when followed up for six months. However, in 2005, another Italian group found no benefits in a larger population of non insulin treated type 2 diabetic people(172). This trial contained more people (n=1896) aged 62.4 years, who were followed up for much longer (3 years). The same Italian group had previously demonstrated in a study of 3567 people with type 2 diabetes of all ages that only people who were able to adjust their insulin doses (which requires regular glucose testing) had better glycaemic control. Other participants who tested their blood glucose at least once per day had higher levels of stress, worry and depressive symptoms, without improved glycaemic control(173). In 1993, a retrospective study of 229 patients conducted on Veterans in the U.S., did not show any improvement in overall blood glucose measurement using either urine or blood testing(174). A further cohort study of 8668 Veterans published in 1997 did not demonstrate any overall benefit in glucose levels in those who used intensive glucose regimes, although each trial participant conducted over 300 home glucose tests per year(175). Two studies from Britain which assessed different treatments did not find any benefit in overall blood glucose level or quality of life in people treated with insulin. The UKPDS 37 which assessed quality of life in a sub group of the trail population showed that the presence of microvascular or macrovascular complications, rather than the type of treatment, affected quality of life (176). Another study from Salford, UK which studied 1000 diabetic people aged over 60 also showed quality of life was not improved with intensive treatment options(177). A study from Bournemouth (U.K.) which assessed only newly diagnosed type 2 diabetic people, found no difference between levels of glycosolated haemoglobin, at 12 months between those people testing their urine and those testing their blood for glucose(178). A meta analysis by Coster *et al* (179), compared blood or urine monitoring with no monitoring and compared blood monitoring with urine monitoring. Using data from four randomised controlled trails comparing urine or blood glucose testing against no testing, there was a non significant decrease in glycated haemoglobin of -0.25% (95%CI, -0.61-0.10%). When three trials were used to compare blood glucose and urine glucose monitoring the estimated reduction in glycated haemoglobin obtained using blood testing was -0.03% (95%CI, -0.52-0.47%).

For glucose testing to be affective, it is presumed that it should be performed regularly. It appears, however, that most diabetic people, regardless age, do not test their glucose regularly. This has been confirmed by three large epidemiological studies(172;180;181). The 2005 Italian study (previously mentioned above) demonstrated that most diabetic people tested their blood glucose less than once per day(172). The NHANES study found that 58.9% of their cohort tested their blood glucose either never or less than once per month(180). The Kaiser Permanente diabetic study showed that people in their cohort aged over 65 years, tested their blood glucose less than once per day, odds ratio 1.3 (1.1-1.5), (less than daily vs daily)(181).

Due to the lack of conclusive benefits and the high financial cost of blood glucose testing there have been suggestions for the increased use of urinary glucose testing(182). Urine testing may be particularly appropriate in diabetic people on diet or tablet treatment alone(182) who do not have the ability to regulate their treatment in conjunction with any glucose results obtained. It should be noted that some diabetic people have been found to hold strongly negative views about urine glucose testing(183) and that blood glucose testing has the ability to empower diabetic individuals(182).

4.2.4 Hypoglycaemia

Hypoglycaemia is defined as a blood glucose measurement below 3.3 mmol/l. Symptoms of hypoglycaemia may be experienced at this level or below. Levels less than 2.5 mmol/l will almost always be symptomatic. The MRC trial did not ask about hypoglycaemia confirmed by blood glucose measurement. It simply asked whether an individual had ever experienced hypoglycaemia.

As well as preventing hyperglycaemia, the use of diabetic medication (sulphonlyurea medications and insulin) can produce hypoglycaemia. Patients need to be aware of the symptoms of hypoglycaemia, how it arises, how to prevent it and how to treat it. Hypoglycaemia is of particular importance in the elderly and can be particularly hazardous. Older people are particularly susceptible to hypoglycaemia and often are not aware of the symptoms(184). In a study of 80 year olds from Marsala (Italy), 124 different people were hospitalised for hypoglycaemia over a two year period(185). Only 10 of these people performed regular blood glucose testing. In the study authors opinion greater numbers of severe hypoglycaemic episodes could have been prevented by teaching the principles of blood glucose measurement.

Older diabetic people at risk of hypoglycaemia need to know how to manage their disease if they are unwell. The reasons for this are two fold. The intake of food causes blood glucose to rise, normally counteracted by oral medication or insulin. If an individual is not eating or is vomiting the intuitive response to a lack of intake would be to decrease medication to prevent hypoglycaemia. The natural physiological response of any individual when they become ill is, however, to produce more glucose through a combination of different physiological pathways. In a non diabetic person, their own insulin production would continue to regulate their blood glucose concentration. In a diabetic individual they do not have the ability to do this. Therefore, the combined action of potentially decreasing medication, in an environment where medication should be maintained or often increased, can easily lead to ever increasing glucose levels. The days which diabetic people are unwell are commonly known as "sick days". What to do on "sick days" is therefore very important. Diabetic people on medication need to be aware they should never stop their medication, may need to increase their medication and should be aware that they may need to seek diabetic advice. Consequently a high degree of understanding is required by diabetic individuals to safely manage their disease. The level of diabetes understanding among an elderly population has never been assessed on this scale before and this thesis provided an interesting insight into the degree of understanding of the disease in an older diabetic population and the factors that were associated with it. It is likely that some older diabetic individuals have poor understanding of the every day management of their condition, which may be exacerbated in those with cognitive impairment(95;186;187). In diabetic populations of all ages a critical review of 19 studies concluded that it was likely that diabetes was associated with an increased risk of cognitive dysfunction(186). A community based survey in the U.K showed that older diabetic people were more likely than non diabetic people to have cognitive impairment(187). Sinclair *et al*(95) studied 396 diabetic people aged over 65 years and compared them with 393 age matched controls. The study showed diabetic people were more likely to have cognitive impairment than non diabetic people (OR 0.54, p<0.001). People with cognitive impairment were less likely to be involved in diabetes self care (self medication and self monitoring) or attend a diabetes clinic.

4.2.5 The use of specialities allied to diabetic care

The use of specialists allied to diabetic health care, such as diabetic specialist nurses, dieticians, eye specialists and chiropodists are widely believed to aid in the overall quality of care of the diabetic patient and increase patient knowledge about the condition(188). Diabetes specialist nurses provide a wide range of support for people with diabetes, especially at the time of diagnosis. They educate patients about injection technique, the correct use of home glucose monitoring, all aspects of hypoglycaemia, education for "sick days" and are a point of patient contact for any aspect of diabetic care. Dieticians provide advice regarding weight loss and suitable diet. Both diabetic specialist nurses and dieticians form an integral part of the diabetic team recommended by the NSF(4). While the exact service provision will vary locally, all diabetic people should have access to these services, if appropriate.

The foot is susceptible to disease in diabetic people, as discussed in section 3.2.3. The guidelines produced by the Royal College of Physicians for the management of the diabetic foot, suggested that in the uncomplicated diabetic foot, yearly surveillance is required(167). The same report admits that due to the disparity of the services available, little reliable data on the use of health care facilities for the diabetic foot exists(167). Adequate monitoring, self care, foot hygiene, awareness of fungal infections, cutting toe nails regularly and correctly, wearing properly fitting shoes and identifying early disease in the foot are all important(167;189). Chiropody aids in correct foot management of the diabetic person in all of these areas. Evidence from two small studies in the UK suggested that the elderly, including those in institutional care, have a particularly low uptake of foot care services. In Leeds, 100 elderly inpatients with diabetes were surveyed and only 50% had seen a chiropodist within the last 12 months(169). Only 20 of 109 (18%) of residents with diabetes in institutional care in Liverpool had had their feet examined in the last year(190).

Diabetic eye disease is easily detectable and is often treatable, especially diabetic retinopathy. The exact management of diabetic eye disease may vary locally between different health care providers; with regular screening from either optician, ophthalmologist or diabetologist. The guidelines developed by the National Institute for Clinical Excellence(166), as part of the NSF(4), recommended examination of the eyes at diagnosis of diabetes and then annually for individuals without pre-existing eye disease. The presence of diabetic eye disease requires review by an ophthalmologist, the frequency of which depends on the type and severity of the diabetic eye disease(166). Screening for diabetic retinopathy is both cost effective and leads to decreased morbidity from diabetic eye disease(46;191-193). Proliferative diabetic retinopathy, the most severe form of diabetic retinopathy, is a very serious disease. Depending on the exact location within the eye, over 50% of people with this condition will be blind within two years(194;195). Retinal laser treatment, which is the treatment of this condition, is also extremely affective, with up to a 60% reduction in the rate of severe visual loss expected(194;195). Diabetes also contributes to other forms of eye disease. For example, cataracts are more common in people with diabetes. Regular eye examination would therefore also detect additional eye disease associated with diabetes. The frequency of eye examination in a large community based diabetic population has not been assessed in an older age group. The Leeds survey of 100 inpatients with diabetes found 52% underwent annual eye examination(169) and in the Liverpool survey of diabetic people in institutional care, 72% had had an eye examination within the last year(190).

Ultimately, the aim of diabetes care is to prevent morbidity and mortality. The point of home glucose testing and dietician review is to improve glycaemic control and minimise microvascular, macrovascular and hypoglycaemic end points. Likewise, regular foot and eye examination is designed to prevent foot ulceration and diabetic retinopathy. There is little evidence that the use of home glucose testing, foot and eye examination actually achieves those aims in patients of any age. In the older person, however, the evidence is sparser still and this thesis provided an ideal opportunity to assess those aims.

4.3. Methods; Classification and Identification of the management and patient understanding of diabetes

This section only included the 1047 participants who were aware that they had diabetes. This figure included diabetic people who did not correctly report diabetes but not individuals identified as having diabetes using a high random glucose. The 130 individuals with diabetes identified using high random glucose were unaware of their health status and therefore would not see anybody about their condition or utilise any health care provision available for diabetes. They were therefore not included in the analysis in this section. The questions 38c to 38m of the detailed questionnaire were used in this chapter (see appendix 2, page 15).

There were two basic questions regarding diabetes management; who was looking after the individuals diabetes and what treatment they were taking. The questions and responses were;

- "Who do you normally see about your diabetes (can be more than one person)?" The responses were "Family doctor/GP", "Hospital doctor", "Practice/District nurse" and "No one".
- "What treatment are you on for your diabetes? (Tick all that apply)". The potential answers were; "diet alone", "tablets", "insulin injections" or "no treatment".

Two questions related to home glucose testing, the answers were "yes" or "no";

- "Do you ever test your blood for sugar?"
- "Do you test your urine for sugar?"

The results were then combined to show participants who did any form of testing. As highlighted above, the benefits of any home blood testing have not been fully established, the type of testing even less so. It was important to determine whether or not a difference existed between blood testing, urine testing or indeed, any form of testing.

Therefore, the groups used for home glucose testing in the remainder of the chapter were; blood testing (any), urine testing (any) and any testing. Blood testing included people who only tested their blood or blood *and* urine. Likewise, urine testing included people who only tested their urine or urine *and* blood. Any testing is the group that includes any form of testing (blood, urine or a combination of both). The frequency of testing was then assessed.

It is unlikely that a person with a MMSE below 23 could meaningfully conduct and/or understand the result of home blood testing. The detailed assessment could be completed by a proxy responder, either partially or totally. In an individual with cognitive impairment proxy response is likely to indicate a closely involved carer. Proxy responses were therefore assessed in the people with cognitive impairment. The degree of cognitive impairment for people who tested home glucose was then assessed.

The questionnaire instructed the nurse conducting the interview to only ask participants who were receiving tablets or insulin to answer the following set of questions. These questions related to hypoglycaemia and its management. The responses were "yes", "no" or "don't know". The questions were;

- "Have you ever had a low blood sugar (a"Hypo")?"
- "If you have a low blood sugar, should you increase your diabetes treatment?"
- "If you have a low blood sugar should you take a sugary drink or snack?"

- "If you have the flu, should you stop taking your diabetes tablets/insulin?"

Regardless of whether an individual has had a hypoglycaemic attack, all of these responders should still be aware of what to do if they ever did have one and know what to do if they became unwell.

The use of specialities allied to diabetic health care was then assessed for the diabetic population. The three questions contained within the detailed questionnaire were;

- "In the last year have you had your feet examined?"
- "In the last year have you had your eyes examined?"
- "In the last year have you discussed your diet with a dietician?"

For each question, the possible responses were "yes", "no", "don't know" or missing. If a response to any of these questions was don't know or missing, it assumed that no meaningful examination had taken place. The responses were then assumed to be no.

4.4. Results

The results are presented for the 1047 people who had a diagnosis of diabetes.

4.4.1 Source of medical advice and treatment regimes

Table 4.1 shows the medical supervision that participants were receiving and the treatments which the diabetic participants were taking. It was possible for participants to record more than one response to either of these questions. Multiple responses occurred if more than one person was responsible for their care or they were on a combination of treatments.

The results for the people who saw only one medical practitioner for their diabetes care demonstrated that 229 (21.87%) people only saw their general practitioner for their diabetes care, 100 (9.55%) only saw the hospital doctor and 155 (14.80%) only saw a nurse for their diabetes management (not shown in the table).

There were 645, out of the population of 1047, people who were taking either tablets, insulin or a combination of both. All of these people had the ability to become hypoglycaemic. There were 501/1047 (47.85%) people taking tablets alone, 112/1047 (10.70%) taking insulin alone and 32/1047 (3.06%) taking a combination of tablets and insulin. These results are not shown in the table.

	General practitioner (GP)	Hospital doctor	Nurse	GP and hospital doctor	GP and nurse	Hospital doctor and nurse	GP, hospital doctor and nurse	No one
Who do you normally see about your diabetes? (Can be more than one) **n=1047** (*Missing=0*)	655 (62.56%)	239 (22.83%)	569 (54.35%)	104 (9.93%)	379 (36.20%)	92 (8.79%)	57 (5.44%)	32 (3.06%)
	Diet Only	Tablets	Insulin	Diet and tablets	Diet and insulin	Tablets and insulin	Diet, tablets and insulin	No treatment
What treatment are you on for your diabetes? (Can be more than one) n=**1047** (*Missing=0*)	373 (35.63%)	533 (50.91%)	144 (13.75%)	63 (6.02%)	2 (0.02%)	32 (3.06%)	1 (0.01%)	27 (2.58%)

Table 4.1. Medical supervision and treatment for diabetic participants who were aware of their condition

4.4.2 Type and frequency of home glucose testing

In total 681/1047 (65.04%) people did some form of glucose testing at home. The results are given for blood testing only, urine testing only, testing of both blood and urine; "blood any", "urine any" and "any testing". The results for home glucose testing are presented in table 4.2. The age distribution, sex and cognitive impairment (MMSE<=23) are also presented for people who did any form of testing. Those who tested their glucose at home were younger ($p=0.001$) and less likely to have a MMSE under 24 ($p<0.001$) than those who did no form of testing. There were 130 (19.09%) people with a MMSE<=23 who reported testing their blood at home. The proportion with cognitive impairment is less in this sub population than the whole diabetic population ($p<0.001$). There were 235 (22.45%) within the whole diabetic population with a MMSE<=23. Proxy responses were made for 42/235 (17.87%) of the diabetic people with cognitive impairment. These results are shown in table 4.3.

Considering only the 645 individuals who were receiving diabetic medication capable of inducing hypoglycaemia the degree of glucose testing was higher than the overall diabetic population ($p<0.001$). There were 493/645 (72.39%) people testing their glucose (blood or urine) in this group. Of these people, 225/645 (34.88%) were testing their blood glucose.

Type of glucose testing	Number (%) n=1047
(Missing=0)	
None	366 (34.96)
Blood only	169 (16.14)
Urine only	406 (38.78)
Blood and urine	106 (10.12)
Blood (any)	275 (26.27)
Urine (any)	512 (48.90)
Any testing	681 (65.04)

Table 4.2. Type of glucose testing for diabetic participants who were aware of their condition

		Number (%) n=681
Sex	Male	318 (46.70)
	Female	363 (53.30)
Age group	75-79 years	364 (53.45)
	80-84 years	203 (29.81)
	85-89 years	82 (12.04)
	90 plus years	32 (4.70)
Cognitive impairment (MMSE<23)		130 (19.09)

Table 4.3 Sex, age and cognitive impairment for diabetic participants who underwent any form of home testing

Overall, 592 out of 1047 (56.5%) of participants tested either urine or blood once per week or more. Only 178/1047 (17.0%) of people with known diabetes tested their blood or urine once per month or less. Considering the 275 participants who measured their blood glucose, there were 101/275 (36.7%) participants who tested about once per day, 101 (36.7%) who measured it weekly and 73/275 (26.4%) participants who measured their blood glucose less than once per month. In the 512 people who tested their urine, 137/512 (26.8%) tested their urine daily, 253/512(49.4%) tested their urine weekly and 122/512 (23.8%) who tested their urinary glucose less than once per month. Age and sex were unrelated to the frequency of testing for either blood (p=0.32 for age and p=0.87 for sex) or urine (p=0.09 for age and p=0.89 for sex).

4.4.3 Hypoglycaemia and individual understanding of diabetes management

Table 4.4 shows the prevalence of hypoglycaemia. It also demonstrates the level of understanding of the management of hypoglycaemia within this population. The results are shown for the 645 people who were taking diabetic medication or insulin and therefore had the potential to become hypoglycaemic. The incorrect response, don't know or a missing response, all indicate that person possessed inadequate knowledge. As such, they all represented an incorrect response and are shown under the incorrect heading.

Of the 645 people who were taking hypoglycaemic medication, 143 (22.17%) had cognitive impairment (MMSE<=23). There were 21/143(14.68%) of people with cognitive impairment who were taking hypoglycaemic medication who had a proxy response.

		Number (%) **n=645**
`Have you ever had a low blood sugar or "hypo"?	Yes	151 (23.41)
	No	425 (65.89)
	Don't know	20 (3.10)
	Missing	49 (7.60)
If you have a low blood sugar, should you increase your diabetes treatment?	Yes	38 (5.89)
	No	331 (51.32)
	Don't know	230 (35.66)
	Missing	46 (7.13)
	Incorrect	**314 (48.68)**
If you have a low blood sugar, should you take a sugary drink or snack?	Yes	439 (68.06)
	No	32 (4.96)
	Don't know	131 (23.31)
	Missing	43 (6.67)
	Incorrect	**206 (31.94)**
If you have the flu, should you stop taking your diabetes tablets/insulin?	Yes	29 (4.50)
	No	424 (65.74)
	Don't know	148 (22.95)
	Missing	44 (6.82)
	Incorrect	**221 (34.26)**

Table 4.4. Understanding of hypoglycaemia in patients taking tablets or insulin.

4.4.4 Utilisation of diabetic services

Table 4.5 shows the results for foot examination, eye examination and discussion regarding diet with a dietician within the last year. The sex and age distribution of these people is also given in table 4.5. Men were more likely to undergo eye examination ($p=0.03$) and have seen a dietician in the last 12 months ($p=0.02$) when compared to women. Men and women were equally likely to undergo foot examination ($p=0.25$). Participants undergoing eye examination ($p<0.001$) and seeing a dietician within the last 12 months ($p<0.001$) were younger than people who did not use these services. Those undergoing foot examination were the same age as those not undergoing foot examination ($p=0.37$).

There were 729/1047 (69.49%) people who underwent both foot and eye examination within the last year and 263/1047 (25.12%) people who had undergone both examinations *and* seen a dietician within the last 12 months.

		Eye Examination Number (%)	Foot examination Number (%)	Dietician Number (%)
Undertook consultation within the last 12 months **n=1047**	Yes	813 (77.65)	836 (79.85)	326 (31.14)
		n=813	**n=836**	**n=326**
Sex	Male	388 (47.72)	377 (45.10)	168 (51.53)
	Female	425 (52.28)	459 (54.90)	158 (48.47)
Age group	75-79 years	421 (40.60)	419 (50.12)	192 (58.90)
	80-84 years	257 (31.61)	257 (30.74)	95 (29.14)
	85-89 years	102 (12.55)	115 (13.76)	35 (10.74)
	90+years	33 (4.06)	45 (5.38)	4 (1.23)

Table 4.5. Diabetic participants who underwent eye, foot or dietician review and who were aware of their condition, with sex and age distribution

4.4.5 Affect of management and understanding of diabetes on diabetic endpoints

Any home glucose testing (either blood or urine) was assessed in relation to the diabetic end points defined in section 3.4. In those who were taking diabetic medication or insulin, the presence of hypoglycaemia was assessed in relation to home glucose testing. Individuals with missing responses for home glucose testing were assumed to be not testing their glucose. The results are presented in table 4.6. The table shows crude odds ratios for diabetic end points and hypoglycaemia in relation to home glucose testing. The odds ratios were then adjusted for age, sex and poor cognitive function.

The questions regarding eye examination and annual foot examination were compared to the defined end points of poor vision or blindness, and foot ulceration respectively and are shown in table 4.7. The odds ratios have been adjusted for age, sex and cognitive function.

Type of glucose testing	Outcome	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio* (95% CI)	P value (adjusted Wald test)
None		1	1	
Any	Vision <6/18	0.82 (0.57-1.19)	1.08 (0.73-1.62)	0.685
Blood only	Vision <6/18	0.81 (0.50-1.33)	0.92 (0.58-1.46)	0.715
Urine only	Vision <6/18	0.91 (0.65-1.26)	1.08 (0.74-1.58)	0.673
Any	Vision <3/60	0.89 (0.41-1.93)	1.29 (0.59-2.79)	0.514
Blood only	Vision <3/60	0.78 (0.32-1.91)	0.89 (0.38-2.09)	0.792
Urine only	Vision <3/60	0.81 (0.41-1.58)	1.01 (0.49-2.06)	0.976
Any	Proteinuria	0.92 (0.57-1.47)	0.91 (0.58-1.46)	0.717
Blood only	Proteinuria	0.78 (0.50-1.23)	0.78 (050-1.22)	0.267
Urine only	Proteinuria	0.94 (0.61-1.44)	0.94 (0.62-1.43)	0.767
Any	Raised creatinine	0.78 (0.57-1.05)	0.82 (0.61-1.10)	0.186
Blood only	Raised creatinine	1.18 (0.85-1.67)	1.32 (0.91-1.92)	0.14
Urine only	Raised creatinine	0.57 (0.43-0.75)	0.56 (0.43-0.74)	<0.001
Any	Myocardial infarction	1.29 (0.77-2.15)	1.16 (0.71-1.91)	0.548
Blood only	Myocardial infarction	1.24 (0.80-1.92)	1.17 (0.75-1.80)	0.485
Urine only	Myocardial infarction	1.04 (0.70-1.62)	0.99 (0.63-1.55)	0.963
Any	Cerebrovascular accident	0.93 (0.58-1.49)	0.97 (0.61-1.58)	0.928
Blood only	Cerebrovascular accident	1.19 (0.80-2.10)	1.34 (0.82-2.19)	0.232
Urine only	Cerebrovascular accident	0.82 (0.57-1.19)	0.83 (0.57-1.22)	0.344
Any	Foot ulceration	0.91 (0.52-1.62)	0.94 (0.54-1.62)	0.81
Blood only	Foot ulceration	1.12 (0.57-2.20)	1.18 (0.59-2.35)	0.638
Urine only	Foot ulceration	0.88 (0.46-1.66)	0.88 (0.46-1.68)	0.697
Any	Hypoglycaemia	3.35 (1.80-6.23)	3.27 (1.72-6.21)	0.001
Blood only	Hypoglycaemia	4.25 (2.79-6.47)	4.38 (2.87-6.68)	<0.001
Urine only	Hypoglycaemia	0.66 (0.47-0.92)	0.64 (0.46-0.89)	0.01

Table 4.6. Crude and adjusted odds ratios for home glucose testing and microvascular, macrovascular and hypoglycaemic complications *Adjusted for sex, age and cognitive impairment

Examination	Outcome	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio* (95% CI)	P value (adjusted Wald test)
None		1	1	
Foot examination	Foot ulceration	1.44 (0.66-3.14)	1.47 (0.69-3.13)	0.316
Eye examination	Vision <6/18	0.80 (0.51-1.28)	1.12 (0.66-1.89)	0.671
	Vision <3/60	0.62 (0.26-1.49)	0.77 (0.29-2.10)	0.617

Table 4.7. Crude and adjusted odds ratios for foot and eye examination and selected outcomes

*Adjusted for sex, age and cognitive impairment

4.6 Discussion

The results from this chapter provide one of the most comprehensive studies into the management and individual understanding of diabetes in the older person conducted in the U.K.

The results show that the majority of older diabetic people are under some form of medical supervision. Although the frequency of supervision is not recorded, 1015 out of a population of 1047 (96.94%) people were seeing either a doctor, a nurse or a combination, for their condition. Encouragingly, only 32/1047 (3.06%) participants were not seeing a medical professional of any description. This figure is much lower than the 19% of elderly people receiving no medical supervision seen in the Leeds in patient study(169). While our survey is community based, this still represented a more encouraging response and involved far greater numbers of diabetic participants. The results for treatment also showed that elderly people are widely and actively treated in the community, using a combination of diabetic treatment regimes. Only 27 (2.58%) participants were on no treatment whatsoever. Diet was listed as a treatment (either alone or in combination) in 439/1047 (41.93%) people. This shows that these individuals understand that correct diet formed an integral part of their diabetic management.

Hypoglycaemia was recorded using only questionnaire responses about symptoms and they were not confirmed by blood glucose measurements. It is therefore possible that not all of the positive responses were definitely true episodes of hypoglycaemia. However, hypoglycaemia is often relatively easy to identify from symptoms alone. Nonetheless, potential misclassification of hypoglycaemia must be noted as a limitation.

In people who were at risk of hypoglycaemia, there was a far higher amount of blood glucose testing (34.88%) than seen in a similar Italian population. In the Italian study, less than 10% of 80 year olds admitted with hypoglycaemia tested their blood(185). Previous studies have found the frequency of blood testing to be less than daily within diabetic cohorts and the frequency of testing to decrease with age(172;180;181). While these results can not be compared directly because the MRC trial assessed the frequency of testing of blood *and* urine, our results show that a large number of older diabetic people test their glucose regularly. For example, the NHANES study found that 58.9% of their participants tested blood glucose less than monthly(180) and the Kaiser Permanente study showed that people over 65 years tested their glucose less than people under 65 years(181). The MRC trial involved large numbers of subjects (681 (75.04%)) who did some form of home glucose testing. Overall, 56.5% of participants tested their glucose at least weekly and only 17.0% tested their glucose once per month or less. The MRC trial results also suggested that younger people were more likely to test their glucose, however, in people who tested their glucose the actual frequency of testing was not affected by age.

The degree of reported hypoglycaemia was 23.41% in those taking hypoglycaemic medication. This shows clearly that hypoglycaemia is a major problem affecting one in five older people on hypoglycaemic medication. The severity and frequency of hypoglycaemia, however, was not estimated in the MRC study. In relation to the questions regarding the understanding of hypoglycaemia management and "sick days", large numbers gave an incorrect answer. Nearly 50% gave an incorrect answer regarding increasing treatment in the presence of hypoglycaemia. The majority of this figure was comprised of a "don't know" response which was regarded as an incorrect response for the purposes of this study. Over 30% of people did not know how to correctly manage hypoglycaemia by taking a sugary drink or snack and nearly 35% gave an incorrect answer regarding "sick day" management. These figures suggest that education regarding these aspects of diabetes management was either not occurring or was ineffective in the older person.

There were 235/1047 (22.45%) people identified as having cognitive impairment. A large proportion of the 681 subjects who tested their glucose had marked cognitive impairment (MMSE<=23). In all, 130 (19.09%) of these people had a MMSE below this level. There were 143 (22.17%) people taking hypoglycaemic medication who also had a reduced MMSE. This suggests that cognitive impairment was high among older diabetic people who have the capacity for hypoglycaemia and that home testing is unlikely to be reliable. Not only is cognitive impairment common in our study, it has previously been shown to be associated with poor diabetes self care(95). While some of these individuals may have carers, without cognitive impairment, who manage their condition for them, many will not. The measurement of proxy response supported this assumption. The results from the MRC study showed that only 17.87% of the people with diabetes and cognitive impairment had a proxy responder. This figure for proxy response was even lower (14.86%) when the 143 people who were receiving hypoglycaemic medication and had cognitive impairment were considered. On the basis of these results it would seem sensible to recommend regular Mini Mental State Examinations (MMSE) to all diabetic individuals aged over 75 years in order to detect cognitive impairment. Identification of people with poor cognitive function, especially if they are receiving hypoglycaemic medication, must be beneficial to the individual.

Both eye examination and foot examination showed a high uptake, with 77.65% having an eye examination and 79.85% having a foot examination within the last year. In terms of the recommendations by NICE(166) and the Royal College of General Practitioners(167) regarding annual screening, the MRC trial results suggest a very good uptake. The results should help to form a more accurate picture of the amount of screening occurring in the older diabetic person. Both figures are above those seen in smaller studies from Leeds(169) and Liverpool(190), although neither of these two studies were community based. The number of diabetic people seeing a dietician within the last 12 months to discuss their diet is lower (31.14%) than the numbers undergoing eye or foot examination. This is less surprising because, while the dietician is an important part of the diabetic team, annual visits are not currently recommended by the NSF for diabetes(4).

The high uptake of eye examination, foot examination, dietician use and regular medical supervision when compared to other studies is interesting. One potential explanation is possibility that participants in the trial, in keeping with all medical trials were more health aware and therefore more likely to utilise medical services than non trial participants.

There have been numerous studies which have shown little, if any, benefit in outcome with regular home glucose testing(173-

177). While some limited benefit in glycaemic control has been found in subgroups of patients, higher levels of stress, worry and depressive symptoms are also reported. No study has so far identified benefits in microvascular or macrovascular end points. The results from the MRC study also show limited benefit in home glucose testing. It is possible that the lack of positive results seen was due to the sample being too small too detect any benefits, as these were not primary endpoints of the original trial. Also, the assessment of the occurrence of micro or macrovascular end points in relation to home testing is cross sectional and continued longitudinal follow up may have showed benefit. It may also be the case that no benefits in micro and macrovascular outcome are conferred by home testing in older people. The only positive association seen for home testing, was between a raised creatinine and urinary testing; the adjusted odds ratio for having raised creatinine in people who tested their urine for glucose was 0.56. The reasons for this are unknown, however, one explanation would be that people with a raised creatinine constitute an advanced form of diabetic end stage disease. As such, they are likely to have been in regular contact with health care professionals, take hypoglycaemic medication and therefore more likely to have been taught how to perform blood testing rather than urinary testing. End stage renal failure also causes an increased renal glucose loss and patients often require decreased dosage of diabetic medication at this stage of their disease. They are therefore at increased risk of hypoglycaemia, another reason that individuals with raised creatinine are unlikely to solely test their urine and to have been taught home blood glucose testing.

Urine testing was associated with a significantly lower adjusted odds ratio for hypoglycaemia. As urinary testing does not detect hypoglycaemia it is possible that this is an incorrect result. Individuals who test their urine are simply unaware that they are hypoglycaemic as urinary testing will not show this. Conversely, any testing or blood testing was strongly associated with having ever had a hypoglycaemic attack. Obviously it is not the testing itself causing the hypoglycaemia, but that fact that those at risk are taught how to perform blood testing and therefore able confirm the presence of hypoglycaemia using their hand held meter.

Finally, neither annual foot or eye examination was associated with significant changes in the amount of foot ulceration or reduced vision or blindness found in the trial population. It is again possible that these results are spurious due to the lack of diabetic trial participants and the cross sectional nature of the survey. They do, however, suggest that further studies are required to confirm any benefits.

This chapter provided one of the largest community based assessments of the management and understanding of diabetes in the older person ever undertaken worldwide. It shows that the majority of older diabetic people see a medical professional and undergo some form of treatment. It provided an interesting summary of community based provision for elderly diabetic people, an area noted for lack of evidence(167). As this study was conducted before the introduction of the NSF for diabetes, it will be particularly interesting to see if these figures change as the NSF continues its development and implementation. In keeping with previous studies, our results did not show any major benefits in diabetic end points in relation to home glucose testing. While these results may be spurious, further studies should be recommended.

Perhaps the most important results generated from this chapter concerned hypoglycaemia and cognitive impairment. The level of understanding of hypoglycaemia and its management in this population was poor. In addition there was a high prevalence of cognitive impairment throughout the whole diabetic population, including those at risk of hypoglycaemia. Both are areas for concern and potential improvement.

Chapter 5 The relationship between hypertension and diabetes in the older person.

5.1 Summary of objectives

To assess the:

Relationship between hypertension and diabetes in the older person;

Affect of systolic and diastolic blood pressure on diabetic endpoints.

5.2 Background

5.2.1 Introduction

Hypertension and diabetes occur commonly together. Estimates vary, with between 20-80% of people with diabetes being reported as having hypertension(31;196), both during the course of the disease and at the initial presentation of the disease to medical care(197). Hypertension is a major independent risk factor for cardiovascular events, stroke, renal disease and diabetic complications(31;198). In people with diabetes affective blood pressure control has been shown conclusively to prevent the diabetic complications associated with hypertension(33;199;200). Epidemiological studies have helped to define the level of appropriate blood pressure(32;201) and assessed different treatment regimes(202-206). The results of these studies suggested that aggressive treatment of hypertension in individuals with type 2 diabetes should be recommended. However, the bulk of these trials were conducted in middle aged adults, the evidence base for the older adult, with and without diabetes, is far smaller. Furthermore, whether blood pressure (systolic or diastolic) has the same associations with diabetic end points in older people has yet to be established, let alone specific thresholds for treatment.

5.2.2 Hypertension in the older person

Over the past two decades increasing epidemiological information has become available regarding the benefits of treating hypertension in the older person; both the diastolic and the systolic components. However, there is still debate about the merits of treating hypertension in very elderly populations. The evidence of the benefits for treatment in the "young" elderly and the concerns regarding the treatment of the "very" elderly are presented below.

In 1991, the Swedish Trial in Old Patients with Hypertension Study (STOP-Hypertension)(207) was one of the first to show benefits of blood pressure reduction in the general older population. It recruited 1627 elderly patients aged between 70 and 84 years. A mean difference in blood pressure of 19.5 mm Hg systolic and 8.1 mm Hg diastolic was achieved, between the active treatment and placebo groups. Compared with placebo, active treatment significantly reduced the number of primary endpoints (myocardial infarction, stroke and other cardiovascular death) (55.5 vs 33.5 events per 1000 patient years, $p = 0.0031$) and non-fatal stroke or myocardial infarction (31.3 vs 16.8 events per 1000 person years, $p = 0.0081$). Although not a primary endpoint, a reduced number of total deaths in the active treatment group was observed (35.4 vs 20.2 events per 1000 person years, $p = 0.0079$).

Mulrow and colleagues conducted a large survey of 13 trials involving 16564 elderly persons (age 60 years and older) which further supported the benefits of treating hypertension in elderly people(208). They concluded that 18 subjects (95% CI, 14 to 25) needed to be treated to prevent one cardiovascular event (cerebrovascular or cardiac), and found a significant decrease in cardiovascular mortality, with 78 (95% CI, 50 to 180) older people requiring treatment to prevent one fatal cardiac event. A subsequent Cochrane review by the same author concluded that anti hypertensive drug therapy was beneficial. The review compared 15 trials including 21908 elderly subjects, with most subjects aged 60 to 80 years. Cardiovascular morbidity and mortality was reduced; 177 vs 126 events (95% CI of the difference 31 to 73) for cardiovascular morbidity and 69 vs 50 deaths (95% CI of the difference 9 to 31) cardiovascular mortality. Total mortality was reduced; 129 vs 111 deaths (95% CI of the difference 4 to 28)(209).

Until recently, reducing systolic blood pressure was considered to be of less importance than reducing diastolic blood pressure but this no longer appears to be the case(42). The Systolic Hypertension in Europe (Syst-Eur) Trial showed that a reduction in isolated systolic hypertension reduced cardiovascular morbidity and mortality in all older subjects (210;211). Syst-Eur was a double blind trial comparing placebo and combinations of active anti hypertensive medications (starting initially with the long acting calcium channel blocker nitrendipine). All trial participants were aged over 60 years at entry, with a mean age of 70.3 years in the active treatment group.

The Systolic Hypertension in the Elderly Program (SHEP) also provided evidence that reducing isolated systolic hypertension was beneficial for persons aged over 60 years(212). A total of 4736 people with a mean age of 72 years were randomised to receive either a diuretic (plus a β-blocker if needed) against placebo. The relative risk for total stroke (the primary outcome) was 0.63 (95% CI 0.49-0.82, p=0.0003) for the treated group. The relative risk of all cause mortality was non-significantly reduced 0.87 (95% CI 0.73-1.05).

Whether the benefits of treating hypertension in the older adult apply to the very elderly is not clear. There are even concerns that the treatment of hypertension in the very elderly person may be detrimental, especially in those aged above 80 years(213). In STOP, older patients who were randomised to active treatment received less benefit, than their younger counterparts. Participants who were aged over 73 years no longer received significant benefit when compared to their younger counterparts(207). Likewise, the Syst-Eur trial did not postpone death in participants older than 75-80 years(210). In contrast SHEP did find a continued benefit in mortality in patients treated for hypertension who were aged over 80 years(212). In the results of the meta-analysis reported by Gueyffier, the authors identified 1670 people with hypertension aged over 80 years old from seven different trials (including STOP, Syst-Eur and SHEP).(49). The results suggested treatment of hypertension was associated with a 34% reduction in the rate of fatal and non-fatal stroke. Major coronary events showed a non-significant trend towards treatment benefit but there was a non-significant trend of increased total mortality, with a 6% relative excess of death from all causes (95% CI –5 to 18). Bulpitt and Fletcher(214), reported that the positive relationship between blood pressure and mortality at the age of 60 to 69 years changes to become a negative relationship in men over 75 years old and in women over 85 years old, with hypertensive individuals actually living longer. They suggest that the negative relationship in very old people reflects underlying terminal disease (cardiac, respiratory or malignant) in those with low blood pressure, and reflects good cardiac function in those with high blood pressure. The authors were unable to conclude that in very elderly hypertensive people lowering blood pressure would be beneficial. They highlighted the lack of evidence from, and the need for, clinical trials of antihypertensive treatment in the elderly. In a longitudinal study, in 2002, Lernfelt and Svanborg published the effect of blood pressure changes between ages 70 and 90 years(215). It showed people with the lowest blood pressure at 70 survived longest but that this relationship changed with increasing age. Individuals alive at 93 years had higher blood pressures at age 90 years than those who had died. Furthermore, people who had a greater individual systolic blood pressure at age 79 years than at age 70 or 75 years were more likely to survive to the age of 90 years. In order to resolve some of these issues the Hypertension in the Very Elderly Trial (HYVET) was set up in 1994(48). The aim of this trial was to investigate the affect of different treatments (no treatment, a diuretic or an angiotensin converting enzyme inhibitor) on stroke incidence in hypertensive patients over the age of 80 years. Secondary end-points include total cardiovascular mortality and morbidity. The target blood pressures were 150 mmHg systolic and 80 mmHg diastolic. The results of the pilot study were published in 2003(216). The results showed in the combined actively treated groups, the reduction in stroke events (hazard rate) was 0.47 (95%CI 0.24 to 0.93) and the reduction in stroke mortality (hazard rate) was 0.57 (95%CI 0.25 to 1.32). However, as was suggested by the Gueyffier meta-analysis(49), the estimate of total mortality supported the possibility of excess deaths in the active treatment group (hazard rate) 1.23 (95%CI 0.75 to 2.01). The HYVET trial protocol has been slightly revised and now compares placebo against indapamide, plus additional perindopril(217). The full trial is currently underway and the results will be published in due course.

5.2.3 The treatment of hypertension in the older person

There has been a large amount of debate regarding the class of drug which should be used in the treatment of hypertension. In non diabetic adult populations there appears to be no clear benefit between medications over and above the benefit of simply lower blood pressure. For example, a large meta-analysis of 9 randomised trials involving over 62000 people of all ages found no benefits between different antihypertensive medications(218). Another survey, conducted on behalf of the Blood Pressure Lowering Treatment Trialists' Collaboration, used data from 29 trials and 162341 participants and similarly failed to find any difference between medications, in addition to the protection conferred by blood pressure lowering alone(219).

There has been concern that certain antihypertensive medications may actually predispose to the development of diabetes itself(220-222). Thiazide diuretics and β-blocking medications were thought to be especially likely to predispose to its development, with other drugs exerting a neutral, or even protective, effect(220-222). Several large randomised controlled trials of the treatment of hypertension found that new onset diabetes occurred up to 15% more often in the groups receiving combinations of β-blockers and diuretics(206;223;224). In 2004, Padwal and Laupacis performed a large systematic review of this subject and concluded that there was weak evidence to support these claims but that the data was far from conclusive and further well designed trials specifically addressing these issues were required(225).

Consequently the British Hypertensive Society have developed recommendations for the which drugs should be use for the treatment of hypertension. The treatment algorithm they have produced adds medication in a step-wise fashion, based on the best available evidence(226). For people aged over 55 years (or any age for people of black origin) a diuretic or calcium channel blocker are recommended first line treatments. This is based on the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)(223). In a population aged over 55 years, these two drugs lowered blood pressure to a greater extent than ACE-Is. Further trials are currently awaited comparing angiotensin II receptor blocking drugs (ARBs) and β-blocking drugs with Calcium Channel Blockers(226).

The British Hypertension Society also highlighted certain specific points relating to the elderly(226). They noted that much of the evidence base for hypertension in the elderly is derived from the SHEP and the SYST-EUR trials(211;212). As these trials used diuretics and calcium channel blockers as the primary active medications, then these are the medications that should be promoted as beneficial. They also highlight the meta-analysis from Messerli which suggested that β-blockers may not be as affective at reducing strokes, coronary heart disease and all cause mortality when compared to diuretics in older populations(227). Subsequently Losartan (an ARB) has also been shown to be more affective at reducing stroke and cardiovascular mortality in older people with systolic hypertension than β-blockade(224). Therefore the British Hypertension Society suggest that the use of β-blocking medication, as an antihypertensive agent, should be limited in the older person(226).

5.2.4 Hypertension in the diabetic person

The prevalence of hypertension in the diabetic population is roughly twice that of a non diabetic age matched population(62). Ritz estimated that up to 80% of people with type 2 diabetes will suffer from raised blood pressure at some time(31). Hypertension is often present when diabetes in first diagnosed. The UKPDS contained a sub-study, specifically designed to assess blood pressure, known as the Hypertension in Diabetes Study (HDS)(14). The first paper published from the HDS confirmed the high prevalence of hypertension in people presenting with newly diagnosed type 2 diabetes(197). Of 3648 new diabetes presentations, 35% of men and 46% of women had mean blood pressure >= 160 mmHg systolic and/or >= 90 mmHg diastolic.

In the second paper published from the HDS, which considered diabetes endpoints in relation to hypertension, hypertension was found to be a major risk factor for cardiovascular morbidity and mortality(198). The hypertensive group had a mean systolic/diastolic blood pressure of 150/92 mmHg compared to 125/78 mmHg in the normotensive group. The mean age of hypertensive participants was 52 years. The authors suggested that patients with hypertension and diabetes have approximately four times the cardiovascular risk of death than non diabetic non hypertensive subjects.

The beneficial affect of lowering blood pressure on diabetic end points was shown convincingly from the UKPDS 38(33). As part of the UKPDS study, 1148 hypertensive people, with a mean age of 56 years, were allocated to either tight control of blood pressure or to less tight control and followed up for 8.4 years for macrovascular and microvascular endpoints. The 758 patients who were assigned to the tight blood pressure control group achieved a mean blood pressure of 144/82 mm Hg compared to 154/87 mm Hg in the less tight group. In the tight blood pressure group there was a reduction of 24% (95%CI, 8%-38%) in diabetes related end points, 32% (6%-51%) reduction in diabetes related deaths, 44% (11%-65%) reduction in strokes and 37% (11%-56%) reduction in microvascular endpoints. There was a non significant reduction in all cause mortality; 22.4 vs 27.3 deaths per 1000 patients years ($p=0.17$). Using the same population, the UKPDS 69, published in 2004, showed that tight blood pressure reduced the clinical complications of all aspects of diabetic eye disease(35). The benefits of treatment are reflected in Standard 4 of the National Service Framework for Diabetes which states "controlling raised blood pressure in people with diabetes who have co-existing hypertension reduces their risk of developing both microvascular complications and cardiovascular disease"(4).

The British Hypertension Society currently states that the highest level of acceptable blood pressure in people without diabetes is 150 mmHg systolic and 90 mmHg diastolic, although it suggests treatment goals of below 140 mmHg and 80 mmHg(226). In people with diabetes the situation is less clear and no lower threshold for treatment has so far been identified, with several trials showing additional benefits below 130 mmHg and 80 mmHg(32;201). In 1998, the Hypertension Optimal Treatment (HOT study) confirmed that there appears to be no optimum lower limit; the lower the blood pressure the better(201). The diabetic people in the HOT study remained at increased risk for cardiovascular endpoints compared to those without diabetes who had similar blood pressure(228). The UKPDS 36 examined the association between systolic blood pressure and macrovascular and microvascular complications. In the study each decrease in mean systolic blood pressure of 10 mm Hg was associated with reductions in risk of 12% for any complication of diabetes, 15% for deaths related to diabetes, 11% for myocardial infarction and 13% for microvascular complications(32). The study did not find any threshold of systolic blood pressure below which the complications of diabetes did not occur. The lack of a lower threshold and continued benefit with decreasing blood pressure have led to lower blood pressure treatment targets in the diabetic person compared to the non diabetic person. The average blood pressures achieved in the UKPDS are now considered too high. In the UKPDS the "tight" blood pressure control group aimed for blood pressure of <150/<85 mm Hg(229). The mean blood pressure level achieved was 144/82 mm Hg; above today's recommendations(45). In 2004, the American Diabetic Association annual guidelines for the management of hypertension in adults with diabetes recommended 130 mmHg systolic and 80 mmHg diastolic as the maximum levels of blood pressure(196). Diabetic individuals with repeated blood pressure readings higher than these levels are advised to have their blood pressure treated.

5.2.5 The treatment of hypertension in the diabetic person

In people with diabetes weight loss, moderate exercise, moderation of alcohol and stopping smoking have all been shown to reduce blood pressure(230). Current American Diabetic Association guidelines recommend lifestyle measures as the first line of treatment for mild hypertension (130-139 mmHg systolic or 80-89 mmHg diastolic) for the initial three months(196). The addition of drug treatment is recommended when these limits are exceeded, with lifestyle changes encouraged as a continued adjunct to drug therapy(196).

Within diabetic populations much debate has centred around the use of angiotensin converting enzyme inhibitors (ACE-I) (or angiotensin-II receptor blocking drugs (ARBs), derivatives of ACE-I) compared to other forms of antihypertensive drugs. Due to specific effects upon the renin-angiotensin system, additional benefits are believed to be attributable to these classes of drug, over and above simply lowering blood pressure. There is now evidence to suggest that ACE-I and ARBs retard the development and progression of albuminuria and the development and progression of neuropathy(231-234). These drugs are discussed in more detail in chapter 6.

Whether there are additional benefits from the use of ACE-I and ARBs with regards to cardiovascular disease is not clear. The Heart Outcomes Protection Study found benefits in cardiovascular events which were attributed to the drug Ramipril (an ACE-I)(45). It is important to note that this trial was a cardiovascular risk trial, not a hypertension trial and it is not established conclusively that the benefits seen were not simply due to lowering blood pressure rather than the drug itself(230). The Losartan Intervention For Endpoint reduction in hypertension study (LIFE study), which used an ARB, showed evidence of reduced cardiovascular and all-cause mortality when compared to β-blockade(224). Conversely, the UKPDS 39, found no difference between captopril (an ACE-I) and atenolol (a β-blocker) in either drugs ability to successfully reduce diabetic endpoints(235). This finding was supported by the ALLHAT study, that included 12000 people with type 2 diabetes and hypertension and found no addition benefits from the using an ACE-I(223).

Therefore in the hypertensive diabetic person, the key issue remains the treatment of hypertension, regardless of the drug. But, if a choice needs to be made, especially in the presence of diabetic renal disease, an ARB would currently be the drug of choice(226).

5.2.6 Hypertension in the older diabetic person

The evidence base for the older hypertensive diabetic person is primarily based on sub group analysis of the diabetic participants within hypertension trials. In the very elderly the evidence base is less well established

There were 492 people with diabetes in the Syst-Eur study and separate analysis showed particular benefits of treatment in older people with diabetes (aged at least 60 years old). Overall mortality was lowered by 55%, cardiovascular mortality by 76% and strokes by 73% in diabetic people in the active treatment group, which achieved a lower systolic blood pressure, than the placebo group(200). Within the SHEP trial there were 583 people with "non-insulin treated" diabetes. In a separate analysis of these people benefits were seen(199). The five year rate of major cardiovascular events was reduced by 34% in the treated group compared to the untreated group, although the all cause mortality was not significantly reduced (relative risk 0.74 (0.46-1.18 95% CI)).

5.2.7 The treatment of hypertension in the older diabetic person

The recommended blood pressure for people with diabetes of 130 mm Hg systolic and 80 mmHg diastolic applies to all age groups. The American Diabetic Association recommendations simply add "In elderly hypertensive patients, blood pressure should be lowered gradually to avoid complications"(230), without further elaboration. Which complications are to be anticipated is not stated. Likewise the British Hypertension Society make no specific reference to age with regards to their recommendations for the treatment of the diabetic hypertensive person(226). Recently the European Union Geriatric Medical Society (EUGMS) have reviewed the currently available guidelines(39). They suggest that following comprehensive cardiovascular assessment and the exclusion of secondary causes of hypertension treatment should be recommended. They recommend treating blood pressure above 140/80 mmHg in most older diabetic people. In frail elderly people they suggest treatment targets of 150/90 mmHg. No organisation recommends specific hypertensive drugs in the older diabetic person above what is suggested for younger people. The treatments are diuretics and calcium channel blockers as an initial treatment in people aged over 55 years and ACE-I or ARBs in individuals with diabetic renal disease(39;226).

There is little evidence, beyond what is known from younger populations, to suggest that hypertensive medications may cause diabetes in older people. Padwal conducted an observational study into the affects of different classes of anti-hypertensive medications in the elderly (aged at least 66 years). They assessed a total of 76176 older people from 5 large datasets in Canada. His team concluded that in the elderly there was no evidence to support an increased incidence of diabetes with different anti hypertensive medications(236).

The currently recommended levels of acceptable blood pressure would until very recently been considered extremely low, especially the systolic component(42). Whether elderly people are able to tolerate such "low" blood pressure remains to be seen, with adverse drug reactions, such as postural hypotension, a concern amongst clinicians(213).

In order to achieve the ambitious blood pressure targets that are recommended it is often necessary to use combinations of antihypertensive drugs(226). In the HDS over 25% of participants in the "tight" blood pressure group required the use of three or more anti-hypertensive medications to control their blood pressure(237). Polypharmacy in the elderly is common. The affect of large numbers of different anti hypertensive drugs adding further to this burden in the older diabetic adult has not been extensively evaluated. Some evidence supports the use of polypharmacy in the younger diabetic person. In patients with a mean age of 56 years, the UKPDS 37 provided evidence that tight blood pressure control did not adversely affect the quality of life when compared to the less tight group(176). In the tight blood pressure group 29% were taking three or more medications compared to 11% in the less tight group(33). Any potential benefits of treatment in relation to diabetic outcomes must be weighed against the many disadvantages of drug treatment. A situation which is especially important in the older person due to the high incidence of adverse drug reactions.

5.3 Methods; Classification and identification of systolic and diastolic blood pressure

5.3.1 Derivation of systolic and diastolic blood pressure using the detailed questionnaire from the MRC trial

Blood pressure readings were an important part of the MRC trial and attempts were made to measure this in all people undergoing detailed assessment. Page two of the detailed questionnaire addresses and records blood pressure (see appendix 2). In order to standardise blood pressure readings between trial participants all trial nurses were instructed in the procedure by the regional training nurse. Detailed instructions on how to measure blood pressure were included in the trial manual of operations provided to each trial nurse. The blood pressures were recorded using Hawksley Random Zero sphygmomanometers. Repeated readings were performed and the zero error of each sphygmomanometer recorded. All blood pressure readings were recorded to the nearest 2 mmHg. Both seated and standing blood pressure readings were taken. Seated readings were taken after at least 3 minutes rest and repeated after another 3 minutes rest. The average of these 2 readings, adjusted for the zero error, was calculated by the trial nurse who conducted the blood pressure measurement. The results were all inspected before data entry at the London School of Hygiene and Tropical Medicine and any obvious errors were corrected if possible. The standing blood pressure readings did not undergo the same degree of data cleaning and had not been corrected for the zero error after entry into the dataset. There were also a large number of missing entries, presumably because standing presented difficulties in some older people. Therefore the standing blood pressure data was deemed to be potentially unreliable. In the clinical setting seated blood pressure readings are used for the basis of treatment decisions and while standing blood pressures are important in the detection of certain specific conditions, their role in diabetes management is less important. It was for these reasons that only the corrected seated average blood pressure readings were used for the remainder of this thesis.

5.3.2 Groupings of blood pressure used for analysis

Both the systolic and the diastolic blood pressures were grouped. The rationale behind this was to attempt to define discernable, clinically useful and convenient cut off points for the affect of hypertension on diabetic endpoints. The groupings chosen were based around increasing increments of 10 mmHg for both systolic and diastolic blood pressure. The systolic group included all systolic pressures up to 100 mmHg, then increasing groups of 10 mmHg up to 160 mmHg and then all systolic pressures above this. The diastolic group included all pressures up to 70 mmHg, increasing groups of 10 mmHg up to 100 mmHg and then all diastolic pressures above this. The systolic and diastolic groupings and numbers of participants within each group are shown in the results section of this chapter (table 5.1). Systolic and diastolic blood pressures were also treated as a binary variable using the most aggressive currently accepted levels for treatment in the younger diabetic person (130 mmHg systolic and 80 mmHg diastolic(196)) as cut off points.

In the detailed questionnaire question 37 asked participants about a range of previous medical conditions, one of which was high blood pressure (see appendix 2, page 14). Question 37 stated:

"Has a doctor ever told you that you had any of the following? If yes, was that with the last year?"

For high blood pressure the responses were no, yes (within the last year) and yes (but before the last year). To simplify the outcome and to increase statistical power the responses were then regrouped into no or yes (either before or within the last year).

5.3.3 Identification of the anti hypertensive medications used

All the medications that individuals were taking were recorded in the detailed questionnaire. The process of recording drug histories has already been discussed in detail in section 2.1.1. Medications participants were taking at the time of the detailed questionnaire were also available for a limited sample of the trial population from the EMIS dataset. For more detail about this process see section 2.1.4. Both of these datasets were searched for any medication which would lower the blood pressure. While some of these medications may not have been prescribed for hypertension itself they all would have had the affect of lowering blood pressure and hence have a treatment effect. For example, β-blocking medication (which lowers blood pressure *and* slows the heart rate) should have been prescribed for all suitable patients following a myocardial infarction since the mid 1980s, when the first convincing evidence of the benefits of this treatment became available(238). The drugs identified which could lower blood pressure were diuretics, α-blocking drugs, β-blocking drugs, angiotensin-converting enzyme inhibitors (ACE-I), angiotensin-II receptor blocking drugs (ARBs), long acting nitrate medications and calcium-channel blockers. All drugs within each class were considered as an antihypertensive medication with no distinctions made between dose, method of delivery, type or make of drug. The number of antihypertensive medications was collated, from zero to three or more.

Due to the potential additional benefits of ACE-Is and ARBs, in respect of diabetic renal disease and the treatment of hypertension, a record was made of the number of people who were receiving these medications. The results are given in section 5.4.3. These results were then discussed in section 6.5, which focused on renal disease in the older diabetic person.

5.3.4 Analysis

The diabetic population with systolic blood pressure above 130 mmHg and diastolic blood pressure above 80 mmHg were described. This was a univariate analysis using the same variables which had previously been used to describe the whole population in chapter 3.

Forward fitting logistic regression models were then created. Potential confounding factors were incorporated into those models if they were found to be associated with increased blood pressure in diabetic individuals from the univariate analysis. Every attempt was made to keep the models as parsimonious as possible. The factors which affected the model by at least five percent were included in the final model.

5.4 *Results*

5.4.1 Distribution of systolic and diastolic blood pressure

Systolic blood pressure was normally distributed and showed minimal skewness (skewness=0.18). The range was 60 mmHg to 258 mmHg, which was considered to represent a normal distribution of true readings. The mean systolic blood pressure for all participants was 148.63 mmHg (standard deviation 22.39), using 14912 readings. The distribution is shown in figure 5.1 below. A normal distribution curve has been overlaid on the figure. Evidence of digit preference can be seen in the marked drop in readings at the 160 mmHg point.

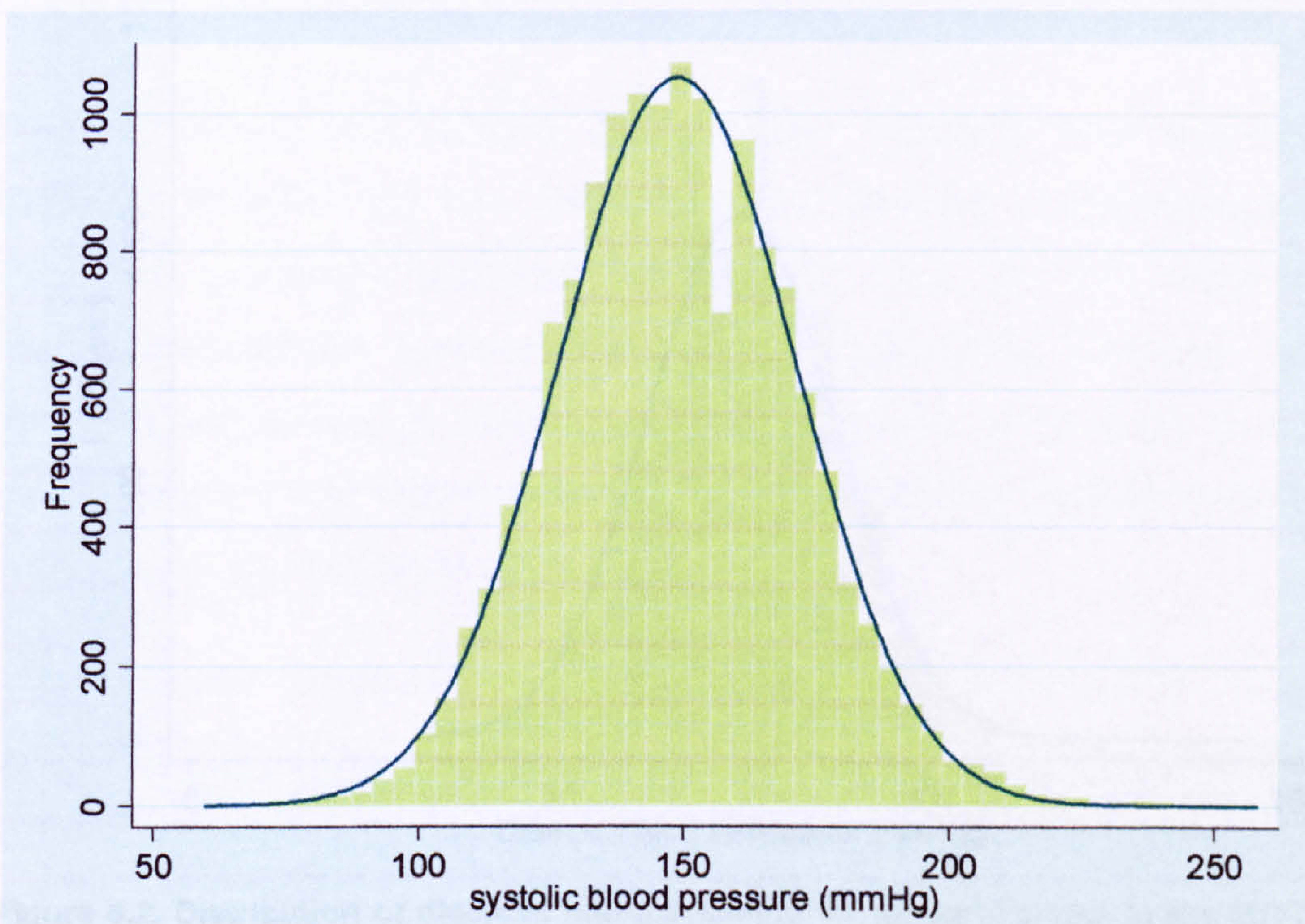


Figure 5.1 Distribution of systolic blood pressure for all participants in the MRC trial

There was a non significant difference (p=0.29) in the systolic blood pressure between people with and without diabetes; 149.3 mmHg (148.27-149.99) versus 148.57 mmHg (148.20-148.95) respectively.

Diastolic blood pressure data revealed 18 readings less than 30 mmHg. These were deemed to be inappropriately low and reclassified as missing diastolic blood pressure readings. Regardless, diastolic blood pressure still appeared to be normally distributed (skewness=0.02), using 14885 valid readings. The three central readings (70, 75 and 80 mmHg) are all lower than expected, which may reflect digit preference. See figure 5.2. A normal distribution curve has been overlaid on the figure.

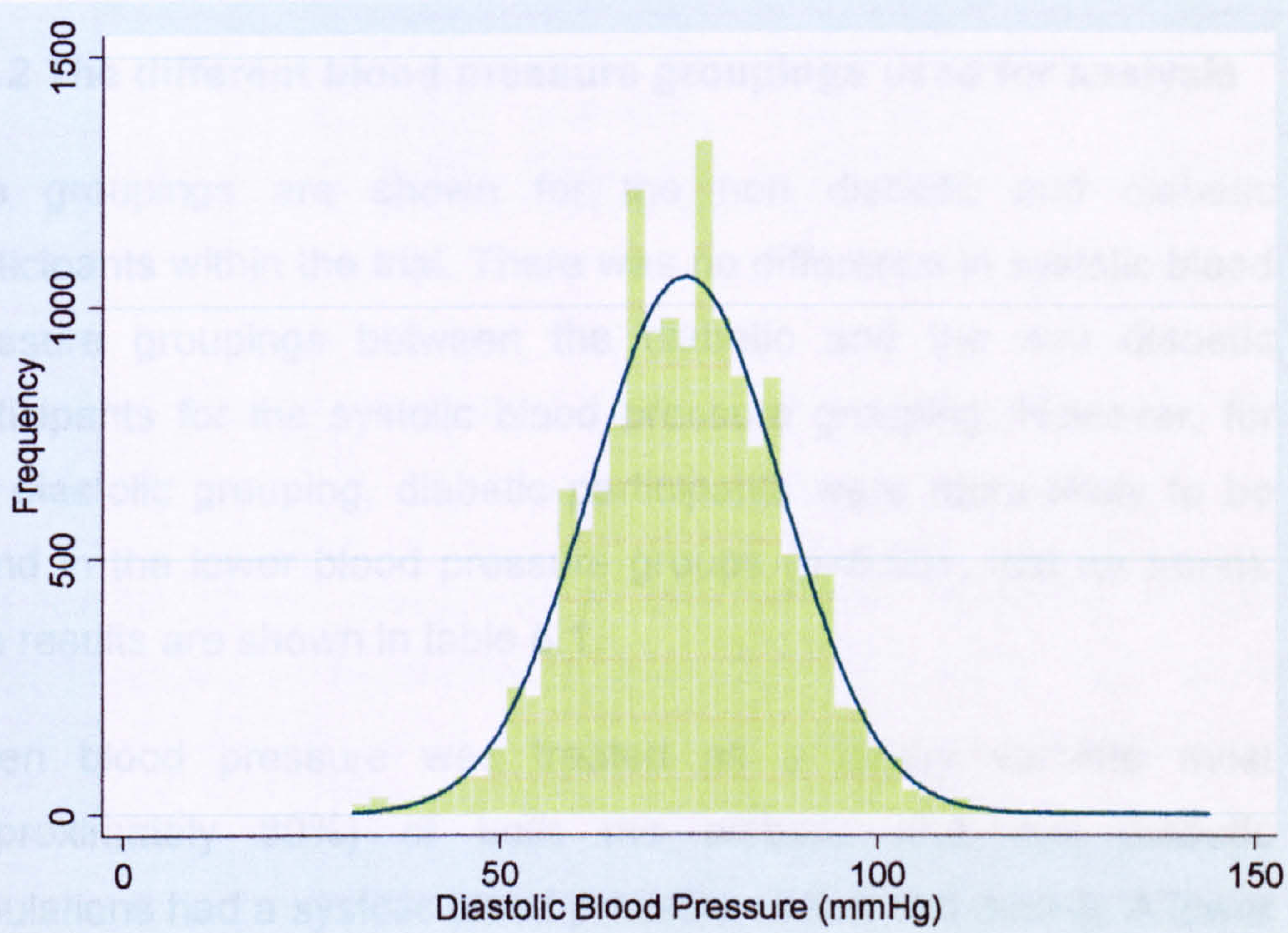


Figure 5.2. Distribution of diastolic blood pressure for all participants in the MRC trial

The range of values was 30.5 mmHg-144 mmHg. The mean for the whole population was 74.59 mmHg (standard deviation 12.75). When comparing those with and those without diabetes the diastolic blood pressure was lower in people with diabetes ($p<0.001$); 73.16 mmHg (72.46-73.87) versus 74.72 mmHg (74.51-74.93) respectively.

There were only 183 (1.21%) participants with missing systolic blood pressure, of whom 13 had diabetes. There were 192 (1.27%) participants with missing diastolic blood pressure, of whom 13 had diabetes. There were no differences between age and sex between either diabetic or non diabetic people with and without missing data (systolic or diastolic).

5.4.2 The different blood pressure groupings used for analysis

The groupings are shown for the non diabetic and diabetic participants within the trial. There was no difference in systolic blood pressure groupings between the diabetic and the non diabetic participants for the systolic blood pressure grouping. However, for the diastolic grouping, diabetic participants were more likely to be found in the lower blood pressure groups ($p<0.001$, test for trend). The results are shown in table 5.1.

When blood pressure was treated as a binary variable most (approximately 80%) of both the diabetic and non diabetic populations had a systolic blood pressure above 130 mmHg. A lower proportion of the total population (approximately 30%), had diastolic blood pressure above 80 mmHg. The results are shown below in table 5.1.

	All participants	Non diabetic participants	Diabetic participants
	n=14912 (%)	**n=13748 (%)**	**n=1164 (%)**
Systolic "10" grouping			
upto 100 mmHg	146 (0.98)	134 (0.97)	12 (1.03)
100-109 mmHg	354 (2.37)	336 (2.44)	18 (1.55)
110-119 mmHg	897 (6.02)	832 (6.05)	65 (5.58)
120-129 mmHg	1530 (10.26)	1408 (10.24)	122 (10.48)
130-139 mmHg	2305 (15.46)	2134 (15.52)	171(14.69)
140-149 mmHg	2550 (17.10)	2341 (17.03)	209 (17.96)
150-159 mmHg	2507 (16.81)	2306 (16.77)	201 (17.27)
160 mmHg and above	4623 (31.00)	4257 (30.96)	366 (31.44)
Systolic "binary" grouping			
upto 130 mmHg	2927 (19.63)	2710 (19.71)	229 (19.67)
130 mmHg and above	11985 (80.37)	11038 (80.29)	935 (80.33)
	n=14885 (%)	**n=13722 (%)**	**n=1164**
Diastolic "10" grouping			
upto 70 mmHg	5087 (34.18)	4636 (33.79)	452 (38.78)
70-79 mmHg	4608 (30.96)	4235 (30.86)	373 (32.07)
80-89 mmHg	3437 (23.09)	3210 (23.39)	227 (19.52)
90-99 mmHg	1403 (9.43)	1311 (9.55)	92 (7.91)
100 mmHg and above	350 (2.35)	330 (2.40)	20 (1.72)
Diastolic "binary" grouping			
upto 80 mmHg	9695 (65.13)	8871 (64.65)	850 (73.02)
80 mmHg and above	5190 (34.87)	4851 (35.35)	314 (26.98)

Table 5.1 Groupings of systolic and diastolic blood pressure

5.4.3 Past history and drug history of hypertension of trial participants

The results of the responses to the question regarding a past medical history of hypertension were 9899 (65.58%) "no", 5029 (33.32%) "yes" and 167 (1.11%) missing. After searching the drug histories from the detailed questionnaire and the drug histories available from the EMIS data there were 9334 (61.84%) people out of the total trial population of 15095 taking no blood pressure lowering medication and 5761/15095 (38.16%) people taking one or more blood pressure lowering medications. The people taking one or more medication comprised 3518 (23.31%) taking one medication, 1693 (11.22%) taking two medications and 550 (3.64%) taking three or more medications. When a history of blood pressure was compared with whether individuals were taking any blood pressure medications 1964 (19.84%) of the 9899 people who responded no to a history of hypertension who were in fact taking at least one blood pressure lowering medication. While it is possible that the medication was prescribed for other reasons it made any results generated using this variable subject to potential bias. Therefore only the drug history information was used in subsequent analysis, not the results from the question regarding a recalled history of hypertension.

There were 559 (47.49%) out of 1177 diabetic individuals taking one or more blood pressure lowering medication compared to 5202 (37.38%) of the 13918 non diabetic population, ($p<0.001$). The diabetic population was also more likely than the non diabetic population to be taking a larger number of blood pressure lowering medications; 315 (26.76%) vs 3203 (23.01%) were taking one only, 187 (15.89%) vs 1506 (10.82%) were taking two and 57 (4.84%) vs 493 (3.54%) were taking three or more, ($p<0.001$, test for trend). To ensure that this difference was not a reflection of diabetic people attending their GPs more often than non diabetic people, and thus having an increased rate of detection of hypertension, a comparison was made with the use of a hearing aid. Deafness is associated with increased visits to the GP. Therefore people with a hearing aid would be more likely to have treated hypertension than people without a hearing aid, simply because they attend their GP more frequently. The results showed that this was not the case. People with a hearing aid were as likely as people without hearing aid to have treated hypertension ($p=0.78$).

There were 929 (6.7%) people in the non diabetic population who were taking an ACE-I. In the diabetic population there were 167 (14.2%) of people taking an ACE-I, ($p<0.001$). There were only 12 people in the entire population who were taking an ARB.

5.4.4 Description of the hypertensive diabetic population

There were 1164 diabetic people with systolic and diastolic blood pressure readings available. Each group had 13 missing entries. This population was described in terms of systolic blood pressure above and below 130 mmHg and diastolic blood pressure above and below 80 mmHg.

Diabetic women were more likely than men to have systolic blood above 130 mmHg, adjusted odds ratio 2.67 (1.97-3.61, $p<0.001$). Women also had a higher adjusted odds ratio for diastolic blood pressure above 80 mmHg, 1.46 (1.10-1.94, $p=0.01$). Age had no clear affects on either systolic or diastolic blood pressures, ($p=0.38$ and 0.57 respectively, test for trend). Age and sex were both found to affect the logistic regression models constructed in this chapter and were both included in the final model.

The other associations are all shown in table 5.2 below. The significant associations were between smoking and BMI. When these to variables were tried in the logistic regression models only smoking remained significant. The number of hypertensive medications was also significant within the model. Therefore the models used in the remainder of this chapter for the associations between systolic and diastolic blood pressure and diabetic endpoints were age group, sex, smoking and the number of hypertensive medications used.

	Variable	Systolic Blood pressure above 130 mmHg n=935	Systolic Blood pressure below 130 mmHg n=229	Odds ratio* (95% CI)	P value	Diastolic Blood pressure above 80 mmHg n=314	Diastolic Blood pressure below 80 mmHg n=850	Odds ratio* (95% CI)	P value
Carstairs	1st (least deprived)	156 (16.68)	43 (18.78)	1	(-)	73 (23.25)	146 (17.18)	1	(-)
by quintile	2nd	231 (24.71)	59 (25.76)	0.95 (0.60-1.52)	0.84	72 (22.93)	217 (25.53)	0.88 (0.53-1.47)	0.64
	3rd	213 (22.78)	53 (23.14)	0.95 (0.60-1.49)	test	57 (18.15)	195 (22.94)	0.95 (0.56-1.61)	test
	4th	174 (18.61)	35 (15.28)	1.10 (0.60-2.00)	for trend	29 (9.24)	152 (17.88)	0.94 (0.59-1.50)	for trend
	5th (most deprived)	89 (9.52)	22 (9.61)	0.90 (0.48-1.70)		31 (9.87)	82 (9.65)	0.91 (0.47-1.79)	
	missing	*72 (7.70)*	*17 (7.42)*			*21(6.69)*	*58 (6.82)*		
MMSE	<=23	161 (17.22)	52 (22.71)	1	(-)	54 (17.20)	158 (18.59)	1	(-)
	>23	774 (82.78)	177 (77.29)	0.71 (0.47-1.07)	0.1	260(82.80)	692 (81.41)	0.93 (0.66-1.31)	0.69
	missing	*0*				*0*			
Alcohol	0-21 units (men)	383 (98.44)	148 (98.66)	1	(-)	123 (98.39)	408 (95.90)	1	(-)
	>21 units (men)	6 (1.54)	2 (1.34)	0.57 (0.35-1.79)	0.57	1 (0.81)	10 (2.41)	1.18 (0.53-2.63)	0.67
	0-14 units (women)	545 (99.82)	79 (100)	1	(-)	190 (100)	434 (99.77)	1	(-)
	>14units (women)	1 (0.18)	0	1.61 (0.31-8.47)	0.57	0	1 (0.23)	1.38 (0.50-3.82)	0.65
	missing	*0*				*0*			
Smoking	Never	363 (38.82)	63 (27.51)	1	(-)	132 (42.04)	295 (34.71)	1	(-)
	Ex-smoker	506 (54.12)	135 (58.95)	0.93 (0.64-1.34)	0.04	162 (51.59)	478 (56.24)	0.84 (0.67-1.05)	0.08
	Current	64 (6.84)	30 (13.10)	0.49 (0.29-0.83)	(trend)	20 (6.37)	74 (8.71)	0.65 (0.38-1.13)	(trend)
	missing	*4 (0.34)*	*1 (0.04)*			*0*	*3 (0.35)*		
BMI	<18Kg/m2	5 (0.53)	10 (4.37)	1	(-)	1 (0.32)	14 (1.65)	1	(-)
	18-25	254 (27.17)	78 (34.06)	9.87 (2.14-45.50)	<0.01	61 (19.43)	270 (31.76)	3.80 (0.57-25.26)	<0.001
	25-30	359 (38.40)	72 (31.44)	16.08 (3.79-68.03)	(trend)	124 (39.49)	308 (36.24)	6.88 (0.99-47.47)	(trend)
	>30	232 (24.81)	53 (23.14)	13.78 (3.08-61.67)		106 (33.76)	171 (20.12)	10.05 (1.54-65.57)	
	missing	*85 (9.09)*	*16 (6.99)*			*22 (7.00)*	*87 (10.24)*		
WHR	<0.90 (men)	70 (19.44)	41 (29.71)	1	(-)	18 (15.52)	93 (24.35)	1	(-)
	>0.90 (men)	290 (80.56)	97 (70.29)	1.72 (1.00-2.94)	0.04	98 (84.48)	289 (75.64)	1.68 (0.98-2.90)	0.05
	missing	*0*				*0*			
	<0.85 (women)	217 (42.72)	32 (44.44)	1	(-)	68 (38.42)	181 (44.91)	1	(-)
	>0.85 (women)	291 (57.28)	40 (55.56)	1.06 (0.58-1.94)	0.85	109 (61.58)	222 (55.09)	1.35 (0.93-1.96)	
	missing	*0*				*0*			

Table 5.2. Characteristics and odds ratios among the diabetic population for both systolic and diastolic blood pressures

*adjusted for age and sex

5.4.5 Associations between diabetes and hypertension

Crude and adjusted odds ratios for the association of 10 mmHg levels of systolic blood pressure and diabetes are shown in table 5.3. After grouping systolic blood pressure as a binary variable, there was no association between systolic blood pressure and diabetes. The results were adjusted for age, sex, smoking and the number of blood pressure lowering medications taken.

Outcome	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio* (95% CI)	P value (adjusted Wald test)
Diabetes			
Systolic "10" grouping			
upto 100 mmHg	1	1	(-)
100-109 mmHg	0.59 (0.28-1.29)	0.63 (0.29-1.36)	0.23
110-119 mmHg	0.87 (0.49-1.54)	0.86 (0.48-1.55)	0.61
120-129 mmHg	0.96 (0.54-1.75)	0.97 (0.54-1.77)	0.93
130-139 mmHg	0.89 (0.49-1.63)	0.90 (0.49-1.64)	0.72
140-149 mmHg	0.99 (0.56-1.77)	1.01 (0.57-1.81)	0.95
150-159 mmHg	0.97 (0.55-1.62)	1.00 (0.57-1.74)	0.99
160 mmHg and above	0.96 (0.54-1.70)	1.02 (0.57-1.79)	0.95
Systolic "binary" grouping			
upto 130 mmHg	1	1	(-)
130 mmHg and above	1.07 (0.93-1.23)	1.12 (0.98-1.28)	0.1

Table 5.3 Association between systolic blood pressure groupings and diabetes
* Adjusted for age, sex, smoking and the number of blood pressure medications

Crude and adjusted odds ratios for the association of diastolic blood pressure and diabetes are shown in table 5.4. Increasing diastolic blood pressure was protective for diabetes. What was noticeable were the trends seen for the "10" grouping. The significantly reduced odds ratios were seen for the middle levels of blood pressure and not for the lowest and the highest levels of blood pressure. There was a highly significant result for the "binary" diastolic variable using a cut point of 80 mmHg. Those with diastolic pressures above this were significantly less likely to have diabetes. The results were adjusted for age, sex, smoking and the number of blood pressure lowering medications taken.

Outcome	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio* (95% CI)	P value (adjusted Wald test)
Diabetes			
Diastolic "10" grouping			
upto 70 mmHg	1	1	(-)
70-79 mmHg	0.91 (0.79-1.03)	0.93 (0.81-1.06)	0.27
80-89 mmHg	0.73 (0.63-0.84)	0.74 (0.65-0.86)	<0.001
90-99 mmHg	0.72 (0.58-0.90)	0.75 (0.59-0.95)	0.02
100 mmHg and above	0.62 (0.36-1.09)	0.66 (0.38-1.15)	0.14
Diastolic "binary" grouping			
80 mmHg and above	0.75 (0.66-0.86)	0.77 (0.67-0.88)	<0.001

Table 5.4. Association between diastolic blood pressure groupings and diabetes
* Adjusted for age, sex, smoking and the number of blood pressure medications

5.4.6 Associations between microvascular endpoints and hypertension

The association between hypertension and poor vision

The associations between the different groupings of systolic blood pressure and poor vision (<6/18) are shown in table 5.5. The trial participants without diabetes showed a trend towards a reduced association with each increase in blood pressure group especially for systolic blood pressure >130 mmHg, adjusted odds ratio 0.82 (95% CI 0.72-0.95) p=0.007, i.e. people with higher blood pressure had *less* visual impairment. There were no significant associations seen within the diabetic population. For the diastolic blood pressure reduced odds ratios were also seen in the whole population, especially at higher levels of diastolic pressure (p=0.03, test for trend). Diastolic blood pressure greater than 80 mmHg was also associated with poor vision in the non diabetic population, adjusted odds ratio 0.84 (95% CI 0.73-0.97) p=0.02. For participants with diabetes, diastolic blood pressure was not associated with poor vision. The results are shown in table 5.6.

	Participants without diabetes			Participants with diabetes		
Outcome	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio* (95% CI)	P value	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio* (95% CI)	P value
Poor vision						
Systolic "10" grouping						
upto 100 mmHg	1	1	(-)	1	1	(-)
100-109 mmHg	0.67 (0.36-1.23)	0.59 (0.30-1.17)	<0.001	0.53 (0.06-4.98)	0.47 (0.05-4.26)	0.47
110-119 mmHg	0.63 (0.39-1.02)	0.60 (0.36-1.00)	test	0.71 (0.10-4.79)	0.68 (0.09-5.00)	test
120-129 mmHg	0.53 (0.35-0.86)	0.53 (0.30-0.91)	for trend	0.55 (0.10-3.10)	0.49 (0.08-3.12)	for trend
130-139 mmHg	0.49 (0.32-0.75)	0.48 (0.30-0.78)		0.67 (0.13-3.58)	0.66 (0.11-3.92)	
140-149 mmHg	0.45 (0.29-0.70)	0.43 (0.26-0.72)		0.62 (0.11-3.66)	0.64 (0.10-4.11)	
150-159 mmHg	0.47 (0.30-0.72)	0.45 (0.28-0.75)		0.50 (0.09-2.82)	0.50 (0.09-2.89)	
160 mmHg and above	0.56 (0.34-0.91)	0.50 (0.30-0.87)		0.64 (0.12-3.30)	0.59 (0.11-3.31)	
Systolic "binary" grouping						
upto 130 mmHg	1	1	(-)	1	1	(-)
130 mmHg and above	0.84 (0.73-0.96)	0.82 (0.72-0.95)	0.007	0.99 (0.63-1.57)	1.05 (0.66-1.67)	0.82

Table 5.5 Association between systolic blood pressure groupings and poor vision

*Adjusted for age, sex, smoking and blood pressure lowering medications

Outcome	Participants without diabetes			Participants with diabetes		
	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio* (95% CI)	P value	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio* (95% CI)	P value
Poor vision						
Diastolic "10" grouping						
upto 70 mmHg	1	1	(-)	1	1	(-)
70-79 mmHg	0.76 (0.64-0.90)	0.86 (0.73-1.02)	0.03	1.15 (0.72-1.82)	1.20 (0.75-1.94)	0.89
80-89 mmHg	0.71 (0.58-0.88)	0.78 (0.64-0.96)	test	0.98 (0.64-1.51)	1.11 (0.72-1.72)	test
90-99 mmHg	0.79 (0.65-0.95)	0.88 (0.72-1.07)	for trend	2.13 (1.19-3.81)	1.98 (1.12-3.48)	for trend
100 mmHg and above	0.54 (0.30-0.94)	0.53 (0.29-1.89)		0.40 (0.05-3.23)	0.39 (0.05-3.29)	
Diastolic "binary" grouping						
upto 80 mmHg	1	1	(-)	1	1	(-)
80 mmHg and above	0.81 (0.69-0.94)	0.84 (0.73-0.97)	0.02	1.14 (0.79-1.63)	1.18 (0.82-1.71)	0.37

Table 5.6. Association between diastolic blood pressure groupings and poor vision

*Adjusted for sex, age, smoking and the number of blood pressure medications taken

The association between hypertension and proteinuria

The associations between systolic and diastolic blood pressure values and proteinuria are shown in tables 5.7 and 5.8 respectively. For participants with and without diabetes there were no significant associations seen between systolic blood pressure and proteinuria. For diastolic blood pressure, no associations between diabetes and proteinuria were seen in the non diabetic population (p=0.11). Within the diabetic population increasing diastolic blood pressure showed a significant trend towards predicting proteinuria (p=0.02). This was also seen in diabetic people with a diastolic blood pressure over 80 mmHg, adjusted odds ratio 1.49 (95% CI 1.05-2.14) p=0.03.

The association between hypertension and raised creatinine

The associations between systolic and diastolic blood pressures and creatinine are shown in tables 5.7 and 5.8 respectively. In the non diabetic population increasing systolic blood pressure was associated with less raised creatinine (p<0.01, test for trend). In people with systolic blood pressure over 130 mmHg the adjusted odds ratio was significantly lower than those with blood pressure below this level, 0.82 (95%CI 0.72-0.92) p<0.01. For the non diabetic population diastolic blood pressure did not seem to be associated with hypertension. There were no associations seen in the diabetic population between either systolic or diastolic blood pressure and raised creatinine.

Outcome	Participants without diabetes Crude Odds Ratio (95% CI)	Participants without diabetes Adjusted Odds Ratio* (95% CI)	P value	Participants with diabetes Crude Odds Ratio (95% CI)	Participants with diabetes Adjusted Odds Ratio* (95% CI)	P value
Proteinuria						
Systolic "10" grouping						
upto 100 mmHg	1	1	(-)	1	1	(-)
100-109 mmHg	1.02 (0.51-2.07)	1.07 (0.54-2.14)	0.47	0.40 (0.05-2.96)	0.47 (0.06-3.75)	0.26
110-119 mmHg	0.97 (0.48-1.97)	1.03 (0.51-2.08)	test	0.40 (0.10-1.67)	0.45 (0.10-1.83)	test
120-129 mmHg	1.04 (0.55-1.99)	1.12 (0.59-2.17)	for trend	0.57 (0.16-2.02)	0.68 (0.18-2.65)	for trend
130-139 mmHg	0.80 (0.39-1.64)	0.86 (0.42-1.78)		0.51 (0.13-1.97)	0.61 (0.15-2.42)	
140-149 mmHg	0.86 (0.43-1.74)	0.91 (0.45-1.84)		0.60 (0.16-2.23)	0.69 (0.18-2.71)	
150-159 mmHg	0.87 (0.44-1.74)	0.95 (0.48-1.90)		0.57 (0.15-2.18)	0.67 (0.17-2.70)	
160 mmHg and above	1.07 (0.52-2.17)	1.16 (0.56-2.41)		0.79 (0.23-2.66)	0.94 (0.27-3.35)	
Systolic "binary" grouping						
upto 130 mmHg	1	1	(-)	1	1	(-)
130 mmHg and above	0.91 (0.75-1.11)	0.92 (0.75-1.15)	0.49	1.23 (0.85-1.76)	1.25 (0.87-1.80)	0.22
Raised creatinine						
Systolic "10" grouping						
upto 100 mmHg	1	1	(-)	1	1	(-)
100-109 mmHg	0.47 (0.31-0.72)	0.53 (0.35-0.82)	<0.01	0.78 (0.11-5.29)	1.72 (0.20-14.60)	0.62
110-119 mmHg	0.45 (0.30-0.68)	0.52 (0.33-0.83)	test	0.74 (0.18-3.11)	0.85 (0.16-4.65)	test
120-129 mmHg	0.42 (0.27-0.66)	0.54 (0.33-0.88)	for trend	0.81 (0.20-3.27)	0.99 (0.19-5.36)	for trend
130-139 mmHg	0.36 (0.23-0.60)	0.48 (0.29-0.81)		0.65 (0.18-2.31)	1.01 (0.23-4.41)	
140-149 mmHg	0.35 (0.22-0.53)	0.45 (0.29-0.70)		0.69 (0.19-2.45)	1.01 (0.23-4.48)	
150-159 mmHg	0.32 (0.21-0.50)	0.44 (0.27-0.73)		0.76 (0.22-2.63)	1.11 (0.26-4.71)	
160 mmHg and above	0.31 (0.20-0.48)	0.44 (0.28-0.71)		0.59 (0.16-2.09)	0.96 (0.22-4.25)	
Systolic "binary" grouping						
upto 130 mmHg	1	1	(-)	1	1	(-)
130 mmHg and above	0.72 (0.64-0.82)	0.82 (0.72-0.92)	<0.01	0.83 (0.61-1.11)	1.02 (0.74-1.42)	0.88

Table 5.7 Association between systolic blood pressure groupings, proteinuria and raised creatinine

*Adjusted for age, sex, smoking and blood pressure lowering medications

Outcome	Participants without diabetes Crude Odds Ratio (95% CI)	Participants without diabetes Adjusted Odds Ratio* (95% CI)	P value	Participants with diabetes Crude Odds Ratio (95% CI)	Participants with diabetes Adjusted Odds Ratio* (95% CI)	P value
Proteinuria						
Diastolic "10" grouping						
upto 70 mmHg	1	1	(-)	1	1	(-)
70-79 mmHg	0.86 (0.73-1.01)	0.89 (0.75-1.06)	0.11	1.51 (0.93-2.43)	1.53 (0.97-2.39)	0.02
80-89 mmHg	0.91 (0.74-1.11)	0.95 (0.76-1.20)	test	1.56 (0.91-2.69)	1.60 (0.95-2.69)	test
90-99 mmHg	0.92 (0.69-1.21)	0.97 (0.72-1.31)	for trend	2.23 (1.19-4.16)	2.30 (1.25-4.25)	for trend
100 mmHg and above	1.47 (0.99-2.17)	1.53 (1.02-2.31)		3.09 (1.31-7.30)	3.11 (1.25-7.69)	
Diastolic "binary" grouping						
upto 80 mmHg	1	1	(-)	1	1	(-)
80 mmHg and above	1.02 (0.85-1.21)	1.05 (0.87-1.27)	0.61	1.47 (1.04-2.11)	1.49 (1.05-2.14)	0.03
Raised creatinine						
Diastolic "10" grouping						
upto 70 mmHg	1	1	(-)	1	1	(-)
70-79 mmHg	0.79 (0.72-0.87)	0.90 (0.81-1.01)	0.26	1.01 (0.74-1.37)	1.13 (0.81-1.58)	0.45
80-89 mmHg	0.73 (0.63-0.85)	0.86 (0.74-1.00)	test	0.74 (0.49-1.10)	0.91 (0.60-1.36)	test
90-99 mmHg	0.74 (0.64-0.86)	0.92 (0.80-1.07)	for trend	0.73 (0.41-1.28)	0.77 (0.42-1.40)	for trend
100 mmHg and above	0.83 (0.58-1.18)	1.03 (0.73-1.46)		1.74 (0.71-4.28)	2.19 (0.79-6.09)	
Diastolic "binary" grouping						
upto 80 mmHg	1	1	(-)	1	1	(-)
80 mmHg and above	0.83 (0.74-0.92)	0.93 (0.83-1.04)	0.18	0.78 (0.55-1.09)	0.87 (0.62-1.24)	0.44

Table 5.8 Association between diastolic blood pressure groupings, proteinuria and raised creatinine

*Adjusted for sex, age, smoking and the number of blood pressure medications taken

5.4.7 Associations between macrovascular endpoints and hypertension

The association between hypertension and angina

For the systolic blood pressure the only significant result recorded was a reduced effect, for individuals in the non diabetic population, with blood pressure above 130 mmHg, adjusted odds ratio 0.77 (95%CI 0.69-0.85, $p<0.001$). The results are shown in table 5.9.

The diastolic results, shown in table 5.10, showed a decreasing odds ratio for angina with increasing group of diastolic blood pressure, within the non diabetic population ($p<0.001$, test for trend). This affect remained, in the non diabetic population, with a diastolic blood pressure above 80 mmHg, adjusted odds ratio 0.77 (95%CI 0.68-0.86) $p<0.001$. For the diabetic people the results were less striking but still present to some extent, for both the grouped blood pressures and when blood pressure was treated as a binary variable.

The association between hypertension and myocardial infarction

Increasing systolic blood pressure was strongly associated with a decreasing odds ratio for myocardial infarction. The association was strongest in the non diabetic population but was still seen in the diabetic population, $p<0.001$ and $p=0.03$ respectively. Systolic blood pressure greater than 130 mmHg was associated with a decreased adjusted odds ratio of 0.67 (95%CI 0.56-0.80) $p<0.001$ for the non diabetic population and 0.46 (95%CI 0.29-0.72) $p=0.001$, for elderly people with diabetes. The results are shown in table 5.9.

Within the non diabetic population increasing diastolic blood pressure was associated with a lower odds ratio for myocardial infarction ($p<0.001$, test for trend). A diastolic blood pressure above 80 mmHg showed an adjusted odds ratio of 0.65 (95%CI 0.57-0.76) $p<0.001$ for myocardial infarction. For the people with diabetes no trend was seen with increasing the diastolic blood pressure. However, having a diastolic blood pressure above 80 mmHg was significantly associated with a lower adjusted odds ratio for myocardial infarction, 0.64 (95%CI 0.43-0.97) $p=0.04$. The results are shown in table 5.10.

Outcome	Participants without diabetes Crude Odds Ratio (95% CI)	Participants without diabetes Adjusted Odds Ratio* (95% CI)	P value	Participants with diabetes Crude Odds Ratio (95% CI)	Participants with diabetes Adjusted Odds Ratio* (95% CI)	P value
Angina						
Systolic "10" grouping						
upto 100 mmHg	1	1	(-)	1	1	(-)
100-109 mmHg	1.06 (0.62-1.81)	1.20 (0.66-2.16)	0.07	1.37 (0.31-7.60)	1.86 (0.30-1.66)	0.25
110-119 mmHg	1.03 (0.63-1.67)	1.11 (0.66-1.86)	test	1.37 (0.24-7.83)	2.44(0.46-12.88)	test
120-129 mmHg	0.83 (0.53-1.29)	0.96 (0.60-1.54)	for trend	1.16 (0.21-6.34)	1.98 (0.40-9.75)	for trend
130-139 mmHg	0.79 (0.51-1.24)	0.92 (0.57-1.48)		1.48 (0.30-7.13)	2.64 (0.57-12.19)	
140-149 mmHg	0.65 (0.41-1.02)	0.74 (0.46-1.19)		1.61 (0.32-8.02)	2.77 (0.61-12.64)	
150-159 mmHg	0.68 (0.43-1.10)	0.80 (0.48-1.32)		1.28 (0.24-6.66)	2.26 (0.47-10.99)	
160 mmHg and above	0.65 (0.42-1.01)	0.76 (0.48-1.21)		0.87 (0.16-4.57)	1.55 (0.32-7.45)	
Systolic "binary" grouping						
upto 130 mmHg	1	1	(-)	1	1	(-)
130 mmHg and above	0.74 (0.66-0.83)	0.77 (0.69-0.85)	<0.001	1.01 (0.74-1.39)	1.08 (0.76-1.52)	0.67
Myocardial Infarction						
Systolic "10" grouping						
upto 100 mmHg	1	1	(-)	1	1	(-)
100-109 mmHg	0.53 (0.29-0.96)	0.57 (0.29-1.15)	<0.001	(-)**	(-)**	(-)**
110-119 mmHg	0.47 (0.28-0.79)	0.52 (0.31-0.87)	test	0.30 (0.07-1.18)	0.55 (0.16-1.87)	0.03
120-129 mmHg	0.39 (0.24-0.67)	0.51 (0.29-0.90)	for trend	0.37 (0.11-1.38)	0.64 (0.20-2.10)	test
130-139 mmHg	0.37 (0.22-0.65)	0.48 (0.27-0.86)		0.27 (0.07-1.09)	0.50 (0.15-1.64)	for trend
140-149 mmHg	0.30 (0.18-0.52)	0.36 (0.20-0.65)		0.13 (0.03-0.54)	0.22 (0.06-0.82)	
150-159 mmHg	0.28 (0.17-0.47)	0.35 (0.20-0.64)		0.15 (0.04-0.56)	0.24 (0.07-0.79)	
160 mmHg and above	0.23 (0.14-0.39)	0.30 (0.17-.53)		0.11 (0.02-0.54)	0.20 (0.04-0.90)	
Systolic "binary" grouping						
upto 130 mmHg	1	1	(-)	1	1	(-)
130 mmHg and above	0.62 (0.52-0.74)	0.67 (0.56-0.80)	<0.001	0.44 (0.29-0.66)	0.46 (0.29-0.72)	0.001

Table 5.9 Association between systolic blood pressure groupings, angina and myocardial infarction

*Adjusted for age, sex, smoking and blood pressure lowering medications, ** no participants had an m.i. in this group

Outcome	Participants without diabetes Crude Odds Ratio (95% CI)	Adjusted Odds Ratio* (95% CI)	P value	Participants with diabetes Crude Odds Ratio (95% CI)	Adjusted Odds Ratio* (95% CI)	P value
Angina						
Diastolic "10" grouping						
upto 70 mmHg	1	1	(-)	1	1	(-)
70-79 mmHg	0.86 (0.76-0.98)	0.89 (0.78-1.01)	<0.01	0.66 (0.46-0.95)	0.66 (0.46-0.95)	0.02
80-89 mmHg	0.70 (0.59-0.83))	0.72 (0.61-0.85)	test	0.70 (0.45-1.11)	0.70 (0.45-1.11)	test
90-99 mmHg	0.75 (0.63-0.89)	0.78 (0.65-0.93)	for trend	0.42 (0.23-0.76)	0.42 (0.23-0.76)	for trend
100 mmHg and above	0.56 (0.39-0.81)	0.61 (0.42-0.89)		0.62 (0.20-1.90)	0.62 (0.20-1.90)	
Diastolic "binary" grouping						
upto 80 mmHg	1	1	(-)	1	1	(-)
80 mmHg and above	0.75 (0.67-0.85)	0.77 (0.68-0.86)	<0.001	0.72 (0.52-0.99)	0.73 (0.52-1.04)	0.07
Myocardial Infarction						
Diastolic "10" grouping						
upto 70 mmHg	1	1	(-)	1	1	(-)
70-79 mmHg	0.79 (0.67-0.92)	0.85 (0.71-1.01)	<0.01	1.02 (0.62-1.69)	1.11 (0.64-1.93)	0.08
80-89 mmHg	0.61 (0.50-0.73)	0.66 (0.54-0.79)	test	0.53 (0.29-0.98)	0.64 (0.31-1.33)	test
90-99 mmHg	0.46 (0.35-0.60)	0.50 (0.38-0.67)	for trend	0.77 (0.36-1.64)	0.86 (0.39-1.90)	for trend
100 mmHg and above	0.49 (0.28-0.89)	0.57 (0.30-1.07)		0.29 (0.05-1.86)	0.32 (0.05-2.00)	
Diastolic "binary" grouping						
upto 80 mmHg	1	1	(-)	1	1	(-)
80 mmHg and above	0.62 (0.54-0.72)	0.65 (0.57-0.76)	<0.001	0.58 (0.41-0.82)	0.64 (0.43-0.97)	0.04

Table 5.10 Association between diastolic blood pressure groupings, angina and myocaridal infarction

*Adjusted for sex, age, smoking and the number of blood pressure medications taken, **no participants had an m.i. in this group

The association between hypertension and cerebrovascular disease

Increasing systolic blood pressure was not associated with cerebrovascular accidents in either the diabetic or the non diabetic population. The results do not show that significance was being approached for either population; none of the p values approach 0.05 and all of the confidence intervals easily encompass one. The results are shown in table 5.11. Within the non diabetic population there was no association with diastolic blood pressure and cerebrovascular accidents. The diabetic population did show an association with increasing diastolic blood pressure and cerebrovascular accidents, ($p=0.04$, test for trend). The association was not seen when treating diastolic blood pressure as a binary variable (above 80 mmHg), adjusted odds ratio 1.05 (95%CI 0.62-1.77) $p=0.86$. The results are shown in table 5.12.

The association between hypertension and foot ulceration

There was no association between foot ulceration and systolic blood pressure for either the non diabetic population or the diabetic population, in any of the groupings. The results are shown in table 5.11. Increasing diastolic blood pressure did not show any association with foot ulceration in either population. When diastolic blood pressure was treated as a binary variable reduced adjusted odds ratios were seen for both the diabetic and the non diabetic population in people with diastolic blood pressure above 80 mmHg. The adjusted odds ratios were 0.65 (95%CI 0.57-0.76) $p<0.001$ for the non diabetic population and 0.64 (95%CI 0.43-0.97) $p=0.04$ for the diabetic population. The results are shown table 5.12.

Outcome	Participants without diabetes			Participants with diabetes		
	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio* (95% CI)	P value	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio* (95% CI)	P value
CVA						
Systolic "10" grouping						
upto 100 mmHg	1	1	(-)	1	1	(-)
100-109 mmHg	1.09 (0.41-2.90)	1.25 (0.48-3.23)	0.64	**	**	(**)
110-119 mmHg	1.26 (0.54-2.89)	1.46 (0.64-3.32)	test	1.12 (0.10-11.92)	0.75 (0.06-9.87)	0.83
120-129 mmHg	1.09 (0.49-2.45)	1.34 (0.61-2.92)	for trend	0.77 (0.13-4.68)	0.66 (0.09-4.84)	test
130-139 mmHg	1.24 (0.57-2.73)	1.55 (0.72-3.34)		1.38 (0.15-12.86)	1.24 (0.12-13.22)	for trend
140-149 mmHg	1.08 (0.49-2.40)	1.32 (0.62-2.86)		0.85 (0.10-7.40)	0.77 (0.08-7.89)	
150-159 mmHg	1.03 (0.46-2.29)	1.31 (0.60-2.86)		1.15 (0.12-11.04)	1.02 (0.09-11.77)	
160 mmHg and above	1.03 (0.47-2.27)	1.30 (0.60-2.80)		1.20 (0.12-11.12)	1.11 (0.10-12.51)	
Systolic "binary" grouping						
upto 130 mmHg	1	1	(-)	1	1	(-)
130 mmHg and above	0.95 (0.78-1.16)	1.01 (0.82-1.25)	0.93	1.40 (0.69-2.82)	1.59 (0.76-3.35)	0.22
Foot Ulceration						
Systolic "10" grouping						
upto 100 mmHg	1	1	(-)	1	1	(-)
100-109 mmHg	1.33 (0.37-4.83)	1.38 (0.36-5.25)	0.63	0.65 (0.03-14.39)	0.80 (0.02-29.59)	0.9
110-119 mmHg	1.63 (0.51-5.22)	1.77 (0.52-6.03)	test	0.35 (0.07-1.66)	0.43 (0.06-2.98)	test
120-129 mmHg	1.11 (0.41-3.00)	1.25 (0.43-3.62)	for trend	0.77 (0.09-6.13)	1.02 (0.07-15.84)	for trend
130-139 mmHg	1.41 (0.49-4.09)	1.60 (0.51-4.95)			0.26 (0.01-5.12)	
140-149 mmHg	1.21 (0.49-2.96)	1.33 (0.51-3.49)		0.61 (0.07-5.74)	0.88 (0.06-14.06)	
150-159 mmHg	1.07 (0.34-3.33)	1.19 (0.35-4.01)		0.46 (0.08-2.63)	0.63 (0.06-6.33)	
160 mmHg and above	0.91 (0.30-2.75)	0.98 (0.30-3.13)		0.41 (0.06-2.94)	0.53 (0.68-2.41)	
Systolic "binary" grouping						
upto 130 mmHg	1	1	(-)	1	1	(-)
130 mmHg and above	0.85 (0.65-1.11)	0.86 (0.65-1.13)	0.27	0.66 (0.34-1.27)	0.70 (0.35-1.40)	0.29

Table 5.11 Association between systolic blood pressure groupings and cerebrovascular accident and foot ulceration

*Adjusted for age, sex, smoking and blood pressure lowering medications, ** no participants had a cva in this group

Outcome	Participants without diabetes			Participants with diabetes		
	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio* (95% CI)	P value	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio* (95% CI)	P value
CVA						
Diastolic "10" grouping						
upto 70 mmHg	1	1	(-)	1	1	(-)
70-79 mmHg	0.96 (0.83-1.11)	1.03 (0.88-1.20)	0.71	1.47 (0.95-2.29)	1.58 (0.99-2.52)	0.04
80-89 mmHg	0.83 (0.70-0.99)	0.91 (0.77-1.08)	test	0.51 (0.23-1.11)	0.55 (0.24-1.26)	test
90-99 mmHg	0.85 (0.61-1.18)	0.94 (0.67-1.32)	for trend	2.39 (1.19-4.80)	2.83 (1.41-5.69)	for trend
100 mmHg and above	1.06 (0.73-1.54)	1.19 (0.81-1.75)		5.26 (1.80-15.37)	5.55 (1.77-17.39)	
Diastolic "binary" grouping						
upto 80 mmHg	1	1	(-)	1	1	(-)
80 mmHg and above	0.87 (0.73-1.03)	0.93 (0.78-1.10)	0.37	0.98 (0.59-1.65)	1.05 (0.62-1.77)	0.86
Foot Ulceration						
Diastolic "10" grouping						
upto 70 mmHg	1	1	(-)	1	1	(-)
70-79 mmHg	0.80 (0.62-1.03)	0.85 (0.66-1.10)	0.21	0.54 (0.23-1.29)	0.52 (0.21-1.28)	0.15
80-89 mmHg	0.87 (0.65-1.17)	0.94 (0.70-1.25)	test	0.40 (0.15-1.08)	0.43 (0.16-1.19)	test
90-99 mmHg	0.73 (0.49-1.09)	0.78 (0.52-1.15)	for trend	1.02 (0.43-2.45)	1.03 (0.42-2.49)	for trend
100 mmHg and above	0.41 (0.14-1.21)	0.43 (0.14-1.25)		**	**	(**)
Diastolic "binary" grouping						
upto 80 mmHg	1	1	(-)	1	1	(-)
80 mmHg and above	0.62 (0.54-0.72)	0.65 (0.57-0.76)	<0.001	0.58 (0.41-0.82)	0.64 (0.43-0.97)	0.04

Table 5.12 Association between diastolic blood pressure groupings and cerebrovascular accident and foot ulceration

*Adjusted for sex, age, smoking and the number of blood pressure medications taken, **no participants had foot ulceration in this group

5.5 Discussion

5.5.1 The relationship between blood pressure and diabetes

The distribution of blood pressure within both populations was normal with apparently lower mean values in the diabetic population. There was no difference between the systolic blood pressure in the non diabetic and the diabetic populations but the diabetic population had lower diastolic blood pressure. The diabetic population was taking more blood pressure lowering medications and taking a larger number of them. It is therefore possible that the lower diastolic blood pressure in the diabetic population was a reflection of the increased number of blood pressure medications being taken. Using the example of hearing aids, it appears that the increased treatment of hypertension was the result of more active treatment of diabetic people by medical practitioners. There were several examples of digit preference in all the blood pressure readings. This is a phenomenon common to trials which record blood pressure manually, leading to systematic bias(239). The problem has diminished somewhat recently due to the increased use of automated blood pressure recordings in clinical trials. But it should be noted as a limitation in the MRC trial but not a serious one.

When the blood pressure was grouped (either in 10 mmHg groups or as a binary variable) systolic blood pressure did not vary between the two populations. For diastolic blood pressure the diabetic individuals were more likely to be in the lower groupings and more likely to have diastolic blood pressure under 80 mmHg. From these results it appeared that hypertension is no more prevalent with the older diabetic population and the diastolic component actually appears to be lower, although probably due to an increased number of medications.

There were just over 80% of (all) participants with a systolic blood pressure over 130 mmHg. Previous estimates suggested that up to 80% of diabetic people will be hypertensive at some point in their illness(31;196). The high number of hypertensive individuals shown by our results reflects the decreasing threshold for the diagnosis of hypertension. The previous estimates were conducted before 130 mmHg was suggested as the upper limit for treatment. If over 80% of the elderly diabetic population are hypertensive then this will have implications if the current guidelines for treatment are to be enforced. All of these people should be treated, either via the initiation of hypertensive medications or additional medications added to their current regime. This would represent a major and potentially detrimental undertaking for many reasons; the financial cost of the drugs, the increased workload of the doctor, increasing polypharmacy and the potential for an increased number of adverse drug reactions. It is important to note that 130 mmHg systolic was used, as a figure of reference, throughout the analysis and the discussion. This figure is the most aggressive target of systolic blood pressure available, and is currently used in America(196). The use of the most aggressive target was justified because the most detrimental effects of excessive treatment, such as polypharmacy, drug interactions and postural hypotension, are more likely to be seen with lower blood pressures (and the increased number of medications needed to achieve those blood pressures). Therefore in order to justify such low blood pressures in the older diabetic person, there needs to be tangible benefits. There did not appear to be any benefit identified from the MRC trial. The EUGMS guidelines suggest 140 mmHg as an upper limit for systolic blood pressure in the older diabetic person(39). The results from the MRC trial did not present any convincing reasons to change the European recommendations.

Increasing systolic blood pressure did not predict the presence of diabetes when it was grouped or treated as a binary variable, although the odds ratios for the higher systolic blood pressures remained over one. It is possible that these results reflect the known higher prevalence of systolic hypertension seen in diabetic populations. Diastolic blood pressure was shown to be protective for diabetes when diastolic blood pressure was treated as a binary variable. When grouped a "J" shaped relationship was seen, with the middle two groups exhibiting protective effects. The results seen for the diastolic blood pressure could again be the result of increased numbers of diabetic people receiving treatment.

5.5.2 The relationship between blood pressure and diabetic microvascular endpoints

Within the non diabetic population there was apparently a marked protective affect between increasing blood pressure and microvascular diabetic end points. Hypertension is established as a risk factor for the development of diabetic eye disease(46) and these results argue against such strong associations in the older person. However, poor vision itself may have prevented people from attending the original trial resulting in under representation and hence selection bias. Another explanation of the results is that diabetic people with poor vision were more likely to be attending medical care than diabetic people without poor vision. Therefore the results seen in the MRC trial were a reflection of increased treatment, due to increased medical attendance in this group.

Increasing diastolic blood pressure showed an association with proteinuria in the diabetic population. Hypertension is an established risk factor for renal disease(33). One would have expected to see the association between proteinuria and systolic blood pressure maintained and the absence of a positive result was surprising. Higher systolic blood pressure was associated with less raised creatinine. Proteinuria is a precursor of end stage renal disease and hence raised creatinine. The lack of association seen may simply reflect patient selection. People with a raised creatinine were more likely to be unwell and hence not take part in original study. Another explanation would be that in the older person, proteinuria is less predictive of the development of renal failure.

5.5.3 The relationship between blood pressure and diabetic macrovascular endpoints

In both populations (people with and without diabetes), increasing blood pressure, systolic and diastolic, grouped or binary, was associated with reduced odds ratios for having angina and myocardial infarction. These associations were lessened for the diabetic persons, but not entirely lost. One possible explanation for these results is that higher blood pressure (systolic or diastolic) reflects a healthy and well functioning myocardium, as suggested by Bulpitt and Fletcher(214). The results argue against lowering blood pressure excessively in the older diabetic person.

Cerebrovascular accidents have been conclusively linked to hypertension and shown to have a decreased incidence with lowering blood pressure(205;207;211). This relationship was only shown from our results for increasing diastolic blood pressure in the diabetic people, with an increasing association seen between stroke and diastolic blood pressure. The higher the diastolic blood pressure the more likely the risk of stroke. The reasons for the lack of association seen between increasing systolic blood pressure and stroke are unclear. In the larger non diabetic population, due to the large sample size, one certainly would have expected to see the association between hypertension and cerebrovascular accident upheld. A possible explanation would have been a lack of trial participation in people who had suffered a stroke, because attendance will have been difficult for these people. More aggressive treatment of hypertension itself in people with a history of stroke seems an unlikely explanation because the results were adjusted for the number of blood pressure medications taken. However, it is possible that people who were deemed at risk of a stroke i.e. people with hypertension, had undergone thorough cardiovascular investigation, including lifestyle advise, lipid profiling and prescribed preventative medications, such as aspirin.

Foot ulceration showed no associations with systolic blood pressure in either population. For both populations there were associations with a decreased odds ratio for increasing diastolic blood pressure. The likely explanation is that this reflects a good cardiac output needed to maintain adequate circulation to the lower limb.

5.5.4 Inherent weaknesses; hypertension and diabetes

The first point of discussion was the use of drug histories to identify people with hypertension. By doing this the hypertensive group should more accurately be described as “the group taking blood pressure lowering medication”. Individuals within this group do not necessarily have high blood pressure. Although they all have a treatment effect. Dosage and exact subclass of drug was also extremely hard to analyse with accuracy. It was also impossible to tell by how much blood pressure had been lowered, if at all.

It was also likely that despite thorough attempts to identify people using this method some people will have been missed. These people would have been those whose medications were not correctly identified at the detailed assessment, either through participant error e.g. if they forgot to bring their correct medications with them or through nurse error e.g. a transcription error when entering the drugs. It was also likely that some of the EMIS data may be erroneous if any drug had failed to have been entered into the EMIS records and hence not identified. Even so identification of participants with hypertension using drug histories still appeared to be more representative than using the question relating to a previous medical diagnosis of hypertension. This was shown by the large number of individuals (19.84%) who denied a history of hypertension who were found to be taking blood pressure lowering tablets. Using drug histories conveyed another advantage. The analysis of the drug history showed that more ACE-I were prescribed in the diabetic population. This implied that the medical profession are aware of potential health benefits of these drugs in diabetic people, and they are being prescribed in elderly populations. The use of ACE-Is and ARBs is discussed in more detailed in section 6.5.

The MRC trial did not recruit people with terminal illness. As has been argued Bulpitt and Fletcher(214) terminal illness was likely to have been associated with the lowest blood pressures. Excluding these people will remove people with low blood pressure and potentially bias the results seen. The extent to which this has affected this dataset is hard to estimate but the distributions of both systolic and diastolic blood pressure were normal. They did not show any obvious absence of lower blood pressure readings.

5.5.5 Cross sectional data

Many of the results obtained in this chapter contradict the established patterns seen in younger patients. Broadly the results of the MRC trial showed that higher blood pressure was associated with less microvascular endpoints and less ischaemic heart disease. The only association which was found to reflect established research was between hypertension and cerebovascular accidents, whose prevalence was associated with an increasing diastolic blood pressure. Several possible explanations for these results have been discussed above in this chapter, however, another explanation which needs to be considered is the nature of the data itself.

The MRC trial used cross sectional data, collected at the time of the detailed screening assessment. This data was used in this chapter to determine the associations between diabetes, hypertension and diabetic endpoints. Cross sectional analysis of diabetes and its complications does not have the power or subtlety to detect differences between the diabetic population and the non diabetic population. A cohort study would have been far more suitable. It would have had the ability to follow diabetic people with and without hypertension and identify any differences in the outcome of diabetic end points. The cross sectional nature of the data analysis may have contributed to the unexpected associations seen between diabetes, hypertension and many of the diabetic end points.

5.6 Conclusions and recommendations

The study shows that a very large number of British elderly diabetic people meet the criteria for treatment of their blood pressure using currently suggested guidelines. However, hypertension did not appear to be more prevalent than in the older non diabetic person and may even be lower, possibly due to increased treatment.

Increasing systolic blood pressure seemed to offer protective affects to the diabetic person and no benefits were conferred for individuals with a systolic blood pressure under 130 mmHg. For the diastolic component, levels above 80 mmHg were predictive of proteinuria only and were protective for other conditions, although the presence of proteinuria and stroke started to increase substantially with diastolic blood pressures over 90 mmHg.

This study did not show conclusive proof of benefits in treating the older hypertensive diabetic person and certainly found no advantages in using the American guidelines, which are the most aggressive. Based on the findings from the MRC study it would be sensible to suggest the use of the European guidelines. However these questions can only be conclusively answered from a randomised controlled trial and this should be the primary recommendation of this chapter.

Chapter 6 The relationship between proteinuria, renal impairment and diabetes in the older person.

6.1 Summary of objectives

To assess the:

Relationship between proteinuria and diabetic end points in the older person;

Relationship between raised serum creatinine (greater than 120 μmol/l) and diabetic end points in the older person;

Relationship between GFR and diabetic end points in the older person.

6.2 Background

6.2.1 Introduction

End stage renal failure (ESRD) is increasing in prevalence(50). Type 2 diabetes is the commonest cause of end stage renal failure and subsequent dialysis in Western Europe(31). Advanced age, male sex and ethnicity have been identified as risk factors for developing renal disease and the progression to end stage renal failure among diabetic people(47;101;104). Established modifiable risk factors include elevated blood pressure, proteinuria, poor glycaemic control and smoking(47;52). Once end stage renal failure has developed in patients with type 2 diabetes the life expectancy is very poor, with higher death rates than non diabetic people. This is due in part from the increased prevalence of cardiovascular disease(50;240). The five year survival rate of ESRD in Germany is 6% and in Australia it is 27%(50). Once ESRD is established the mainstay of treatment is dialysis; either peritoneal dialysis or haemodialysis. Either form of dialysis is a hardship for any age group. This is especially so in the older person and is associated with high morbidity in addition to high mortality(42).

Renal function is measured using blood testing, commonly creatinine and urea. Raised blood levels, of either, indicate an inability of the kidney to excrete them and therefore poor renal function (overt nephropathy). Raised creatinine is regarded as an indicator of chronic renal failure. The Glomerular Filtration Rate (GFR) is a measure of renal function which is derived directly from the creatinine levels, age and sex, and is considered to be a more accurate measure of renal function. Decreasing GFR, reflects worsening renal function. It has been described in more detail in section 3.4.1. This measure is discussed throughout this chapter in conjunction with creatinine. It is important to note that in diabetic renal disease, proteinuria precedes a raised creatinine, that persistent proteinuria is virtually diagnostic of diabetic renal disease and raised creatinine levels (and decreasing GFR) indicate a relatively late stage of disease progression.

The National Service Framework (NSF) for Diabetes(4) does not discuss diabetic renal disease in detail. Diabetic renal disease is simply implicit throughout the document because correct management of the condition is an integral part of two main pillars of the NSF for Diabetes; clinical care of adults with diabetes and the detection and management of long term complications. For example, the NSF for diabetes states, as a key intervention, that treatment of microalbuminuria with ACE-Is reduces the rate of progression to nephropathy.

6.2.2 Renal disease and renal failure, in diabetes

Pathogenesis

Diabetic individuals are at increased risk of non diabetic renal disease(31), with up to 25% of diabetic people undergoing haemodialysis having some known chronic non diabetic disease. It is likely but not certain, that these individuals have worse morbidity and mortality than non diabetic people with the same type of renal disease(31). However, the majority of type 2 diabetic patients have a similar morphological pattern of renal damage and associated micro and macroalbuminuria (proteinuria)(51;241). Microalbuminuria is caused by thickening of the glomerular basement membrane and abnormal function of podocytes within the kidney(51). This is first detected as protein (albumin) in the urine, which leaks through the basement membrane. In the absence of other disease microalbuminuria is diagnostic of diabetic renal disease. Initially a small amount of protein is lost into the urine (microalbuminuria, 30-300mg/day). Without treatment this process can worsen with larger and larger amounts of protein lost into the urine (macroalbuminuria, >0.5g/day). It should be noted that microalbuminuria has been reported to have spontaneously regressed(19) and is not always present in diabetic renal disease(241). Microalbuminuria is, however, the strongest and one of the most easily detectable signs of diabetic renal disease(51). Continuing microalbuminuria reflects continuing structural damage to the kidney. As this process progresses the overall function of the kidney deteriorates (overt nephropathy).

Diabetic renal disease is a condition which occurs over a long period of time, usually many years. Progression varies between individuals but up to 40% of patients with microalbuminuria progress to overt nephropathy(240). The UKPDS 64 estimated the rate of progression from microalbunimuria to macroalbuminuria as 2.8% per year and from macroalbuminuria to raised creatinine as 2.3% per year(34). Once overt nephropathy has been established the rate of decline in GFR is between 2 and 20 ml/min/year(240). After 20 years, 20% of diabetic people with overt nephropathy will have developed ESRD(240). However, with improvements in life expectancy and decreasing mortality from cardiovascular disease more and more people are surviving long enough to develop ESRD(50).

Factors associated with diabetic renal disease

Hyperglycaemia contributes to the development of diabetic renal disease(242) but hyperglycaemia is not a primary focus of this thesis and is not considered further. Hypertension also contributes to the development of diabetic renal disease(33). The diabetic kidney does not regulate intraglomerular pressure correctly allowing systemic hypertension to be transmitted to the glomerulus(242). There can be up to a 20 mmHg increase in glomerular pressure. Flow pressure, renin, angiotensin and cytokines are all thought to contribute to this process and the subsequent renal damage. In mouse models several of the abnormal cellular responses seen in the diabetic kidney are reversed by the use of angiotensin II blockers (ARBs) providing evidence in support of their potential therapeutic benefits (see section 5.2.5 and below)(242). Smoking is also an established modifiable independent risk factor for the development of diabetic renal disease(47). Smokers progress to ESRD approximately twice as quickly as non smokers(47). Unlike other forms of renal disease(243), restriction of dietary protein intake has not been shown conclusively to slow the progression of diabetic renal disease(244).

Prevention of diabetic renal disease

There is growing evidence that the progressive renal impairment seen in diabetes is preventable(47) and potentially reversible(242). In type 2 diabetes the use of ACE-I, given in adequate dosage(245), has been established as a preventative medication but the evidence base for doing so, while substantial, is less than for type 1 diabetes. For example, a study involving 156 people, with normotensive, normoalbuminuric type 2 diabetes showed that progression to albuminuria and decline in renal function was less in people receiving Enalapril compared to placebo. The patients were all under 60 years, with a mean age of 54.9(246). A recent, large, randomised control trial, the Bergamo Nephrologic Diabetes Complications Trial (BENEDICT), also concluded that the use of an ACE-I decreased the incidence of microalbuminuria. They compared ACE-Is alone or in combination with a calcium channel blocker against placebo. The patients were hypertensive, but non microalbuminuric. They enrolled a total of 1204 subjects. The mean age was 61.6 years in the treatment group(247). The diabetic substudy of the Heart Outcomes Prevention Evaluation Study (Micro-HOPE), while primarily a hypertension study, also showed a reduction in progression to overt nephropathy in those receiving Ramipril(45). Weighed against this, the UKPDS 39, found no additional benefits in the use of an ACE-I when compared to β-blockade(235). Also the Appropriate Blood Pressure Control in Diabetes (ABCD) trial found no differences between progression to microalbuminuria and overt albuminuria, when ACE-I and nisoldipine (a calcium channel blocker) were compared to placebo. Both had an equal affect in slowing progress, in both normotensive and hypertensive populations(202;248). Much of the current evidence is summed up by a systematic review of the use of ACE-Is and renal outcomes published in 2004(53). Before describing the results it is important to note some limitations of this review. The analysis used trials which contained patients with both type 1 and type 2 diabetes, subgroup analysis of type 2 analysis was limited due to differences between the trials and each analysis was dominated by the Micro-HOPE study, which contained by far the largest number of participants (1140 in total). The results showed that ACE-Is increased the rate of regression from microalbuminuria to normoalbuminuria (relative risk 3.42, 95% CI 1.95-5.99), using 15 trials and 1888 participants. ACE-I reduced the relative risk for progression from microalbuminuria to macroalbuminuria (0.45, 0.28-0.71), using 16 trials and 2010 participants. The doubling of creatinine was non significantly reduced (relative risk 0.60, 0.34-1.05) using 8 studies and 1868 participants. The development of ESRD was also not reduced (relative risk 0.64, 0.40-1.03), when 9 studies were considered using 1907 participants. The New England Journal of Medicine published three papers consecutively in 2001 which highlighted the benefits of angiotensin II receptor blockade (ARBs) in type 2 diabetic people(232-234). In the first of these studies hypertensive patients with diabetes and urinary protein excretion of at least 900 mg/24hours, aged between 30 and 70 years were studied. The results showed that treatment with Irbesartan conveyed additional benefits, over and above that of simply lowering the blood pressure. The people who received the ARB had a 33% lower (p=0.02) risk of doubling of creatinine than those not receiving the ARB(234). The second study assessed Losartan (an another ARB) in people aged between 31 and 70 years, with diabetic nephropathy irrespective of their blood pressure. The study again showed a reduced incidence of the doubling of the serum creatinine concentration (risk reduction 25%, p=0.006) and reduced progression to ESRD (risk reduction 28%, p=0.002)(233). In the final study, ARBs were shown to reduce the progression of microalbuminuria in patients with hypertension and existing microalbuminuria(232). Patients who received the highest dosage of Irbesartan (300 mg) were less likely to have worsening proteinuria than those on lower doses (150 mg) or placebo. This effect was independent of the blood pressure lowering effect. The authors reached this conclusion because the difference in systolic and diastolic blood pressures between the two treated groups was minimal. The average blood pressures were 144/83 mmHg in the placebo group, 143/83 mmHg in the 150 mg group and 141/83 mmHg in the 300 mg group. They also adjusted for these minimal effects and found that the benefits of higher dose Irbesartan remained. The combination of ACE-I and ARBs have also been assessed and there is currently weak but increasing evidence for additional benefits in preventing renal disease in diabetic people(242;249;250).

6.2.3 Non renal disease in the diabetic person with renal impairment

Diabetic eye disease, cardiovascular and to a lesser extent cerebrovascular disease are all associated with diabetic renal disease. It is estimated that up to 75% of people with diabetic renal disease will also have diabetic retinopathy, with the severity of retinopathy increasing with the degree of albuminuria(251). Retinopathy, has also been linked to the rate of decline in renal function, as an independent risk factor. Small observational studies(252;253) identified a link, which has subsequently been confirmed by a recent large randomised controlled study; the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study (254). The authors of this study conducted a separate analysis of the baseline characteristics of 1513 type 2 diabetic patients with nephropathy. They performed ophthalmoscopy or fundus photography on 1456 (96.5%) participants at baseline to identify retinopathy. Patients with retinopathy had a 52% increase in doubling of serum creatinine ($p<0.001$) and a 47% increased risk of ESRD ($p=0.002$) compared to those without retinopathy.

It has been well established that diabetic renal disease is an independent risk factor for both cardiovascular disease and cardiovascular death(50;240). Microalbuminuria predicts death, an association which strengthens with increasing proteinuria and raised creatinine. Diabetic people with raised creatinine show the largest association with death(65), especially cardiovascular death(128). Cardiovascular death in part accounts for the especially high mortality rates seen in type 2 diabetic people who enter ESRD(50). Therefore much emphasis is placed upon cardiovascular risk management in these people. In a study of people with type 2 diabetes and microalbuminuria intensive intervention aimed at treating multiple cardiovascular risk factors reduced cardiovascular events by 50 percent(255). There is less available evidence linking diabetic renal disease and cerebrovascular disease. Subgroup analysis of the HOPE study(45), found that microalbuminuria was associated with a composite primary endpoint which included stroke. The composite end point consisted of a combined cardiovascular end point of myocardial infarction, stroke and cardiovascular death(256). The UKPDS did not find associations between cerebrovascular disease and diabetic renal disease. The UKPDS 29 found that microalbuminuria did not significantly effect the estimated hazard ratio for the occurrence of stroke(257). The UKPDS 60, which designed a risk engine for the likelyhood of stroke in diabetes, did not include renal disease in their final risk model and does not state whether it was tested(130).

The UKPDS 59 showed that peripheral vascular disease was not associated with albuminuria.. This finding was present both the initial presentation to medical care and following re-assessment at 6 years.

6.2.4 Renal disease in the older person

Increasing age is a risk factor for the development of ESRD of all types. The incidence continues to rise as age increases even into the extremes of old age(258). The increasing prevalence is due to the aging population and improvements in survival leading to renal patients living longer and surviving to older age(259).There is also evidence to suggest that renal replacement therapy, including transplantation, is affective in the older person(260;261). Comparable survival rates have been experienced by "healthy" people aged over 75 years and younger people aged under 40(261). However, there does appear to be prejudice towards the older person when referral rates to renal specialist centres are studied and treatment is often based, in the UK at least, on the quality of life that an individual can expect following treatment(259). Nonetheless, it is encouraging that the rate of renal replacement therapy being offered to the older person is increasing(259).

Cardiovascular disease has also been linked to renal insufficiency in the older person(262). In a large community based survey 5888 adults all aged over 65 years were assessed as part of the baseline assessment in the Cardiovascular Health Study. The authors showed that in people with renal insufficiency compared to people without renal insufficiency, the adjusted odds ratio for clinical or subclinical cardiovascular disease was 1.43 (1.18-1.75)(262).

6.2.5 Renal disease in the older diabetic person

The prevalence of diabetes is increasing, the population is aging and survival in diabetes is improving(60;161). Each of these factors has contributed to diabetic nephropathy becoming a disease of the older person, in a similar manner to which renal disease in general has increased in the elderly population. However, like the majority of issues in the care of the diabetic older person, clinical understanding and practice is based on the extrapolation from younger populations. For example, the current position statement of the American Diabetes Association regarding diabetic nephropathy, makes no specific references to the older person, regarding aetiology or general treatment(240). With the lack of evidence in mind, Wasen and colleagues attempted to characterise renal disease in the elderly(263). Using a cross sectional survey of people aged between 64 and 100 years (mean age 74 years) they identified 187 people with diabetes out of a total population of 1260. They divided the population in two; those under and those over 80 years. In the older age group, simply having diabetes, when compared to hypertension, was a greater determinate for decreased renal function. They suggested that in the older person hypertension may be of less importance to the development of diabetic renal disease than in the younger person.

6.3 Methods

6.3.1 The classification and identification of proteinuria, raised creatinine and Glomerular Filtration Rate

Proteinuria, raised creatinine and Glomerular Filtration Rate (GFR) were described in Chapter 3. The association between these variables and hypertension has also been described in chapter 5. Their relation to mortality is presented in Chapter 8. The results presented here reflect the associations of proteinuria, raised creatinine and GFR with other diabetic endpoints; poor vision, blindness, angina, myocardial infarction, cerebrovascular accident and foot ulceration. The results are presented for the non diabetic population and for the diabetic population.

The 2002 guidelines from the National Kidney Foundation(153) have highlighted two levels of GFR; 60 and 15 ml/min per 1.73 m^2. In the UK renal function is graded into five stages. GFR below 60 ml/min per 1.73 m^2 corresponds to stage 3 (moderate) disease and less than 15 ml/min per 1.73 m^2 corresponds to stage 5 (established renal failure). These two levels of GFR (60 and 15) were also assessed in relation to diabetic end points.

6.3.2 Analysis

The diabetic populations with and without proteinuria and raised creatinine were described. This used the factors which have been used consistently throughout this thesis. Univariate analysis was performed and any significant associations were recorded.

Forward fitting logistic regression models were created incorporating potential confounding factors, identified in the univariate analysis. Every attempt was made to keep the models as parsimonious as possible.

6.4 Results

6.4.1 The description of the diabetic populations with and without proteinuria and raised creatinine

The populations were described in terms of age group and sex. There were no significant associations seen when proteinuria was considered. Raised creatinine was associated with both increasing age ($p<0.01$, test for trend) and sex ($p<0.001$) in the diabetic population. The results are shown in table 6.1.

In table 6.2 the associations between the two diabetic populations are given. The variables used were Carstairs index, MMSE, Alcohol, smoking BMI and WHR. There were no significant associations recorded in either of the populations for any of the variables tested.

When logistic regression models were created for use in the remainder of this chapter only age and sex were found to be significant. Only these two variables were used in the models for both the diabetic populations; proteinuria vs no proteinuria and raised creatinine vs no raised creatinine.

Variable		Proteinuria yes n=188	Proteinuria no n=909	Odds ratio* (95% CI)	P value	Raised creatinine yes n=236	Raised creatinine no n=806	Odds ratio* (95% CI)	P value
Age group	75-79 years	95 (50.53)	459 (50.50)	1	(-)	97 (41.10)	428 (53.10)	1	(-)
	80-84 years	58 (30.85)	283 (31.13)	0.99 (0.67-1.45)	0.96	79 (33.47)	241 (29.90)	1.45 (0.95-2.19)	<0.01
	85-89 years	29 (15.43)	122 (13.42)	1.15 (0.62-2.09)	test	48 (20.34)	97 (12.03)	2.18 (1.42-3.34)	test
	90 plus years	6 (3.19)	45 (4.95)	0.66 (0.25-1.63)	for trend	12 (5.08)	40 (4.96)	1.32 (0.66-2.67)	for trend
	missing	*0*				*0*			
Sex	Male	89 (47.34)	425 (46.75)	1	(-)	151 (63.98)	345 (42.80)	1	(-)
	Female	99 (52.66)	487 (53.25)	0.97 (0.66-1.43)	0.9	85 (36.02)	461 (57.20)	0.42 (0.29-0.61)	<0.001
	missing	*0*				*0*			

Table 6.1. Age and sex characteristics and odds ratios for diabetic populations for both proteinuria and raised creatinine

*adjusted for age and sex

Variable		Proteinuria yes n=188	Proteinuria no n=909	Odds ratio* (95% CI)	P value	Raised creatinine yes n=236	Raised creatinine no n=806	Odds ratio* (95% CI)	P value
Carstairs	1st (least deprived)	38 (20.21)	152 (16.72)	1	(-)	35 (14.83)	151 (18.73)	1	(-)
by quintile	2nd	49 (26.06)	227 (24.97)	0.85 (0.43-1.69)	0.79	60 (25.42)	199 (24.69)	1.53 (0.86-2.74)	0.25
	3rd	35 (18.62)	211 (23.21)	0.65 (0.38-1.12)	test	59 (25.00)	184 (22.83)	1.82 (1.06-3.13)	test
	4th	30 (15.96)	168 (18.48)	0.70 (0.32-1.49)	for trend	40 (16.95)	152 (18.86)	1.56 (0.79-3.10)	for trend
	5th (most deprived)	20 (10.64)	83 (9.13)	0.94 (0.38-2.36)		24 (10.17)	69 (8.56)	1.89 (1.00-3.57)	
	missing	*16 (8.51)*	*68 (7.48)*			*18 (7.63)*	*51 (6.33)*		
MMSE	<=23	37 (19.68)	154 (16.94)	1	(-)	45 (19.07)	137 (17.00)	1	(-)
	>23	151 (80.32)	755 (83.06)	1.24 (0.79-1.93)	0.34	191 (80.93)	669 (83.00)	1.06 (0.72-1.57)	0.32
	missing	*0*				*0*			
Alcohol	0-21 units (men)	87 (97.75)	419 (98.59)	1	(-)	149 (99.15)	342 (99.30)	1	(-)
	>21 units (men)	2 (2.25)	6 (1.41)	1.11 (0.22-5.73)	0.9	2 (0.85)	3 (0.70)	0.50 (0.09-2.85)	0.67
	0-14 units (women)	98 (99.66)	483 (99.59)	1	(-)	85 (100)	459 (99.75)	1	(-)
	>14units (women)	1 (0.33)	2 (0.41)	0.59 (0.14-2.48)	0.46	0	2 (0.25)	1.36 (0.39-4.78)	0.62
	missing	*0*				*0*			
Smoking	Never	64 (34.04)	337 (37.07)	1	(-)	76 (32.20)	287 (35.61)	1	(-)
	Ex-smoker	107 (56.91)	502 (55.23)	1.14 (0.76-1.69)	0.21	142 (60.17)	454 (56.33)	0.80 (0.57-1.13)	0.31
	Current	17 (9.04)	69 (7.59)	1.31 (0.66-2.61)	(trend)	16 (6.78)	64 (7.94)	0.70 (0.39-1.26)	(trend)
	missing	*0*	*1 (0.11)*			*2 (0.85)*	*1 (0.12)*		
BMI	<18Kg/m2	0	15 (1.65)	(-)	(-)	0	14 (1.74)	(-)	(-)
	18-25	56 (29.79)	259 (28.49)	1	0.58	70 (29.66)	226 (28.04)	1	0.46
	25-30	71 (37.77)	343 (37.73)	0.84 (0.61-1.12)	(trend)	95 (40.25)	310 (38.46)	1.63 (0.59-3.48)	(trend)
	>30	47 (25.00)	216 (23.76)	1.02 (0.90-1.14)		52 (22.03)	194 (24.07)	1.08 (0.88-1.32)	
	missing	*14 (7.45)*	*76 (8.36)*			*19 (8.05)*	*62 (7.69)*		
WHR	<0.90 (men)	23 (26.74)	83 (21.17)	1	(-)	32 (23.02)	72 (22.15)	1	(-)
	>0.90 (men)	63 (73.26)	309 (78.83)	0.71 (0.39-1.29)	0.25	107 (76.98)	253 (77.85)	1.09 (0.65-1.84)	0.74
	missing	*0*				*0*			
	<0.85 (women)	37 (40.66)	202 (44.01)	1	(-)	30 (40.00)	190 (43.78)	1	(-)
	>0.85 (women)	54 (59.34)	257 (55.99)	1.13 (0.72-1.79)	0.6	45 (60.00)	244 (56.22)	1.07 (0.56-2.01)	0.84
	missing	*0*				*0*			

Table 6.2. Characteristics and odds ratios for diabetic populations for both proteinuria and raised creatinine

*adjusted for age and sex

6.4.2 The association between microvascular complications and proteinuria and raised creatinine

The examination of microvascular end points (poor vision and blindness) found no associations in the non diabetic population. Neither proteinuria or raised creatinine were associated with either end point, although raised creatinine and poor vision was approaching significance ($p=0.07$). The results can be seen in table 6.3 When considering only the diabetic population, no significant associations were observed using either end point, see table 6.4.

	Outcome	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio* (95% CI)	P value (adjusted Wald test)
Proteinuria		1	1	(-)
	Poor vision	1.18 (0.97-1.43)	0.93 (0.73-1.19)	0.57
	Blindness	1.37 (0.92-2.04)	1.09 (0.69-1.69)	0.72
Renal Impairment		1	1	(-)
	Poor vision	1.31 (1.12-1.53)	1.18 (0.99-1.41)	0.07
	Blindness	0.36 (0.88-2.11)	1.01 (0.65-1.57)	0.96

Table 6.3 Association between proteinuria, raised creatinine and visual impairment in the non diabetic population

*adjusted for age group and sex

	Outcome	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio* (95% CI)	P value (adjusted Wald test)
Proteinuria		1	1	(-)
	Poor vision	0.85 (0.48-1.52)	0.96 (0.57-1.61)	0.87
	Blindness	0.84 (0.37-1.89)	0.51 (0.19-1.38)	0.18
Renal Impairment		1	1	(-)
	Poor vision	1.06 (0.60-1.89)	0.92 (0.54-1.56)	0.74
	Blindness	0.85 (0.32-2.27)	0.73 (0.27-2.01)	0.54

Table 6.4 Association between proteinuria, raised creatinine and visual impairment in the diabetic population

*adjusted for age group and sex.

6.4.3 The association between macrovascular complications and proteinuria and raised creatinine

The non diabetic population demonstrated an association between proteinuria and cerebrovascular accidents, adjusted odds ratio 1.28 (1.03-1.59), $p<0.02$. In the non diabetic population, proteinuria was not associated with angina, myocardial infarction or foot ulceration. The non diabetic population showed consistent associations between raised creatinine and angina, myocardial infarction and cerebrovascular accidents, $p=<0.01$ for each. There were no associations seen between renal impairment and foot ulceration in the non diabetic population. The results are shown in table 6.5.

When the diabetic population was considered, there were no associations seen between proteinuria and any of the macrovascular complications. In this population, renal impairment did not show significant associations between angina, myocardial infarction or foot ulceration. The only significant association was between renal failure and cerebrovascular accidents, adjusted odds ratio 1.68 (1.20-2.35), $p<0.01$. The results are shown in table 6.6.

Outcome		Crude Odds Ratio (95% CI)	Adjusted Odds Ratio* (95% CI)	P value (adjusted Wald test)
Proteinuria		1	1	(-)
	Angina	1.08 (0.89-1.31)	1.11 (0.88-1.39)	0.38
	Myocardial Infarction	1.03 (0.87-1.22)	1.02 (0.84-1.24)	0.85
	Cerebrovascular Accident	1.33 (1.08-1.65)	1.28 (1.03-1.59)	0.02
	Foot Ulceration	1.17 (0.82-1.65)	1.11 (0.75-1.66)	0.57
Renal Impairment		1	1	(-)
	Angina	1.44 (1.28-1.62)	1.17 (1.04-1.33)	0.01
	Myocardial Infarction	2.59 (2.17-3.11)	1.67 (1.37-2.06)	<0.001
	Cerebrovascular Accident	1.91 (1.65-2.21)	1.49 (1.26-1.76)	<0.001
	Foot Ulceration	1.13 (0.84-1.51)	1.06 (0.77-1.47)	0.7

Table 6.5 Association between proteinuria, raised creatinine and macrovascular complications in the non diabetic population

*adjusted for age group and sex.

Outcome		Crude Odds Ratio (95% CI)	Adjusted Odds Ratio* (95% CI)	P value (adjusted Wald test)
Proteinuria		1	1	(-)
	Angina	0.99 (0.66-1.50)	0.98 (0.64-1.50)	0.93
	Myocardial Infarction	0.99 (0.67-1.50)	0.97 (0.63-1.50)	0.89
	Cerebrovascular Accident	1.25 (0.72-2.14)	1.37 (0.79-2.42)	0.26
	Foot Ulceration	0.94 (0.39-2.28)	0.94 (0.39-2.29)	0.89
Renal Impairment		1	1	(-)
	Angina	1.11 (0.75-1.65)	0.97 (0.64-1.48)	0.89
	Myocardial Infarction	1.49 (1.03-2.17)	1.18 (0.79-1.78)	0.41
	Cerebrovascular Accident	1.68 (1.18-2.37)	1.68 (1.20-2.35)	<0.01
	Foot Ulceration	1.36 (0.63-2.93)	1.26 (0.57-2.80)	0.56

Table 6.6 Association between proteinuria, raised creatinine and macrovascular complications in the diabetic population

*adjusted for age group and sex.

6.4.4 The association between Glomerular Filtration Rate (GFR) and diabetic endpoints

When considering GFR it is important to remember that *decreasing* GFR reflects worsening renal function. The results for GFR and diabetic end points showed a continued association between worsening renal function and diabetic end points, particularly macrovascular end points. Statistical significance was achieved in the relationship between both GFR and myocardial infarction and GFR and cerebrovascular disease, among the non diabetic and the diabetic populations. It was also approaching significance (p=0.09) for angina in the non diabetic population. The odds ratios for the association between *increasing* GFR and myocardial infarction and cerebrovascular disease were 0.98 (0.97-0.98), p<0.001 and 0.98 (0.98-0.99), p<0.01 for the non diabetic population and 0.98 (0.97-0.99), p<0.01 and 0.97 (0.96-0.98), p<0.001 for the diabetic population.

There were 6809 (48.92%) out of the 13918 non diabetic people with GFR less than 60 ml/min per 1.73 m^2 and 585/1177 (49.45%) diabetic people with GFR less than 60 ml/min per 1.73 m^2, (p=0.32). The were only 22 (0.14%) of people in the whole trial with GFR less than 15 ml/min per 1.73 m^2. Due to the small numbers statistical results were not reliable and this cut off point was not considered further. When GFR was grouped into those with GFR above and below 60 ml/min per 1.73 m^2 strong associations were seen for the non diabetic population. Visual impairment, blindness, angina, myocardial infarction and cerebrovascular disease all demonstrated significant odds ratios in non diabetic people with GFR less than 60 ml/min per 1.73 m^2, see table 6.7. In the diabetic population only myocardial infarction and cerebrovascular disease were associated with GFR less than 60 ml/min per 1.73 m^2; odds ratio 1.39 (1.02-1.90, p=0.04) and 1.62 (1.12-2.35, p=0.01) respectively. The results are shown in table 6.8.

Please note that all the results for GFR were "unadjusted". Age and sex are used in the calculation of GFR and it was therefore not appropriate to adjusted for them again. The results are shown in tables 6.7 and 6.8.

Outcome		GFR*		GFR 60**	
		Odds Ratio (95% CI)	P value (adjusted Wald test)	Odds Ratio (95% CI)	P value (adjusted Wald test)
Microvascular		1	(-)	1	(-)
	Poor vision	0.98 (0.98-0.99)	0.39	1.44 (1.21-1.71)	<0.001
	Blindness	0.99 (0.98-0.99)	0.69	1.39 (1.00-1.93)	0.05
Macrovascular		1	(-)	1	(-)
	Angina	0.99 (0.99-0.99)	0.09	1.14 (1.02-1.29)	0.03
	Myocardial Infarction	0.98 (0.97-0.98)	<0.001	1.63 (1.42-1.87)	<0.001
	Cerebrovascular Accident	0.98 (0.97-0.99)	<0.01	1.32 (1.16-1.50)	<0.001
	Foot Ulceration	0.99 (0.98-1.01)	0.76	1.10 (0.89-1.37)	0.37

Table 6.7 Association between Glomerular Filtration Rate and diabetic end points in the non diabetic population

*Odds ratios represent each unit increase in GFR

** Odds ratios represent the change from above to below 60 ml/min per 1.73 m2

Outcome		GFR*	
		Odds Ratio (95% CI)	(adjus
Microvascular		1	
	Poor vision	0.99 (0.97-1.00)	
	Blindness	0.99 (0.97-1.01)	
Macrovascular		1	
	Angina	0.99 (0.98-1.00)	
	Myocardial Infarction	0.98 (0.97-0.99)	
	Cerebrovascular Accident	0.98 (0.97-0.99)	
	Foot Ulceration	0.99 (0.98-1.01)	

Table 6.8 Association between Glomerular Filtration Rate and diabe

*Odds ratios represent each unit increase in GFR

** Odds ratios represent the change from above to below 60 ml/min per

6.5 Discussion

The lack of available epidemiological evidence regarding kidney function and diabetes was surprising even by the standards of the diabetic elder. There was only one paper of note published by Wasen et.al(263) that characterised this population in detail and the results from this chapter should therefore add to the available evidence. The reasons for the lack of evidence may be explained by the fact the diabetic renal disease is becoming a disease of the older person whereas previously it was a disease of the younger person. As this population continues to grow, through the continued aging of the population as a whole, increasing diabetes prevalence and improvements in diabetic care, it is likely the published evidence base will continue to expand.

6.5.1 The characteristics of the diabetic populations with proteinuria and raised creatinine

Only male sex and increasing age were shown to affect the relationship been diabetes and raised creatinine. These two factors are established risk factors for diabetic renal disease(47). The lack of other associations seen in both populations was interesting. Not even smoking which has been previously associated with diabetic renal disease showed any association(47). It is possible that this was due to a survivor affect with all susceptible smokers dying before the age of 75 years. Other associations may also have become apparent with larger populations. Despite the absence of positive results the description of these populations forms an interesting cross sectional assessment of these two older diabetic populations.

6.5.2 Proteinuria, raised creatinine and microvascular end points

Interestingly there was no association observed between diabetic eye disease and proteinuria or raised creatinine. Neither proteinuria or raised creatinine showed any significant associations, although significance was being approached for raised creatinine and poor vision in the non diabetic group. This was in sharp contrast to the published evidence suggesting that that diabetic eye and renal disease are closely linked(251). The associations previously observed were between diabetic retinopathy and renal disease. As has been noted elsewhere in this thesis, retinopathy and visual impairment are not the same thing. It was highly likely that many of the diabetic population had retinopathy which had not manifested as worsening vision. Therefore direct comparisons with previous epidemiological evidence concerning diabetic eye disease were not possible. Another explanation for the lack of associations observed was that visual impairment and blindness were both under represented in the trial population as a whole. The physical handicap of reduced vision may have prevented many people from actively participating in the original trial. Visual handicap may also have prevented some people from reading their letters of invitation into the trial and hence they did not participate in the MRC trial.

6.5.3 Proteinuria, raised creatinine and macrovascular end points

The non diabetic population with proteinuria were more likely to have suffered from a cerebrovascular accident than non diabetic people without proteinuria. Proteinuria did not appear to predict other large vessel disease in the non diabetic population. In the non diabetic population the well established associations between large vessel disease and raised creatinine were observed. Angina, myocardial infarction and cerebrovascular accidents all demonstrated a raised adjusted odds ratio. When the diabetic population was considered the only association shown from the MRC trial was between raised creatinine and cerebrovascular accidents. No other associations were seen in the diabetic population in conjunction with renal disease, either proteinuria or raised creatinine.

It was interesting to observe that the only association seen in the diabetic population was between cerebrovascular disease and raised creatinine, not cardiovascular disease and renal impairment. All cardiovascular outcomes have previously been consistently and strongly associated with diabetic renal disease(50;240). Cerebrovascular disease is associated with renal impairment in diabetic people but possibly to a lesser extent(45;256). Why the cardiovascular associations seen in the MRC trial were less strongly associated with diabetes than in previous studies is not clear. The possibility of bias must therefore be considered. One possible explanation for the results seen is premature cardiovascular death. The early death of diabetic people from cardiovascular disease may have prevented these people from surviving into older age; the healthy survivor effect. This implies that these people who have survived are less susceptible to macrovascular end points and may reflect a distinct group of patients, able to survive into older age with diabetes. Could the lack of associations seen have been attributable to improved cardiovascular risk factor management? In clinical practice there is a strong emphasis on cardiovascular risk prevention in renal patients. The MRC trial results were adjusted for the number of hypertensive medications used and smoking did not affect the results of the logistic regression models. However, other factors, which were not assessed as part of the MRC trial, such as adverse lipid profiles, may have been more commonplace in the people with renal disease. This explanation seemed unlikely because the associations between cardiovascular disease and renal disease were still observed in the non diabetic population. One would expect all renal patients to have cardiovascular risk factors managed aggressively, regardless of their diabetic status. The healthy participator effect, common to all clinical trials, is also likely to reduce the incidence of major cardiovascular disease in both populations and may have had the affect of reducing any effects seen.

6.5.4 GFR and diabetic end points

In the non diabetic populations the occurrence of both myocardial infarction and cerebrovascular accidents were associated with worsening renal function, as measured by worsening GFR. The results for angina also approached significance ($p=0.09$). For the diabetic population, both myocardial infarction and cerebrovascular accidents were associated with worsening GFR. The results were even stronger when GFR was grouped into people above and below 60 ml/min per 1.73 m^2. This figure represents a clinically useful measure and corresponds to stage 3 renal disease. Strong associations were seen in the non diabetic population for all diabetic end points with the exception of foot ulceration. This included visual impairment. The associations were weaker in the diabetic population but still present for myocardial infarction and cerebrovascular accidents. The results generated previously in this thesis question the validity of GFR in older diabetic populations (see section 3.9). In chapter 3 of this thesis the results failed to demonstrate a difference in GFR between the diabetic and the non diabetic populations, despite a higher mean creatinine in the diabetic group. The results from this chapter suggest that worsening GFR was a strong predictor of cardiovascular and cerebrovascular disease in diabetic older people.

The low absolute number (22, 0.14%) of people with GFR less than 15 ml/min per 1.73 m^2 presumably reflects the poor health of these people and the inability to enrol in a clinical trial. This group is not discussed again in this thesis.

6.5.5 Diabetic renal disease and peripheral vascular disease

Peripheral vascular disease (represented in the MRC trial by the use of foot ulceration) did not show any associations with diabetic renal disease. There is no biological evidence base for an association between diabetic renal disease and peripheral vascular disease, other than shared risk factors for the development of either condition. The results generated from the MRC trial were in keeping with the results of the UKPDS 59, which did not find that proteinuria or renal impairment was associated with peripheral vascular disease(132). However, as discussed at length in chapter 1, the results of all the UKPDS are hard to extrapolate to the older person because the age of the participants recruited was much younger. Another factor limiting comparison between the two trials is the methods used to identify peripheral vascular disease. The UKPDS 59 identified peripheral vascular disease if two of three of the following criteria were identified in either leg; 1. ankle-arm blood pressure index <0.8, 2. neither dorsalis pedis or posterior tibial pulses were palpable or 3. intermittent claudication was reported. The MRC study collected self reported data on the presence of foot or leg ulcers and used this as a proxy measure for peripheral vascular disease.

6.5.6 Hypertension, hypertensive medications and diabetic renal disease

Hypertension, either systolic or diastolic had little or no affect on any of the odds ratios generated and was not included in the final adjusted odds ratios. Therefore, the only blood pressure variable included in the final model used for the analysis was the number of blood pressure medications being taken. This variable fitted into the models well and was included throughout. As highlighted in Chapter 5 the number of blood pressure medications being taken correlated closely with both systolic and diastolic blood pressure.

The use and number of blood pressure medications and ACE-Is were correlated. There were over 56% of people taking an ACE-I if they were taking three or more medications for hypertension (chapter 5, section 5.4.3); in effect ACE-Is and the number of blood pressure medications represented a similar measure. Both fitted into each statistical model assessing outcomes. However, they added no more together, than alone. Keeping the statistical model as parsimonious as possible led to the use of only the number of blood pressure medications in the final model. Any additional benefits of ACE-I and/or ARBs in diabetic renal function over and above that of simply lowering the blood pressure could therefore not be addressed and therefore remain unknown in this population. It is also worth mentioning that since the MRC trial ended in 1999, the use of ACE-I and ARBs has increased dramatically as the evidence base for benefits of their use has increased. At the time that the MRC trial was conducted there were 167 out of a diabetic population of 1177 (14.2%) who were taking an ACE-I. There were only 12 participants in the original trial identified as taking an ARB, which had only recently been launched as a drug class. The numbers of older people taking both ACE-Is and ARBs is likely to be much higher today. Therefore any results which may have been generated regarding ACE-Is and ARBs would probably have been out of date and not reflect current clinical practice.

6.5.7 Inherent weaknesses

The results generated from this chapter are most striking for the lack of associations seen between renal impairment and diabetic end points. While the lack of available evidence in the older person should be noted, based on younger populations, one would have expected to find more positive associations.

Chapter 5 also showed a lack of association between hypertension and diabetic end points. The two main factors discussed in chapter 5 are also relevant to this chapter; a lack of identification of all diabetic end points and the cross sectional nature of the data.

Using the questionnaire it is possible that several diabetic end points were under represented. Diabetic eye disease may have been under represented because it is difficult for visually impaired people to participate in trials and macrovascular complications may not always have been recorded due to failure to be identified from the questionnaire, although the questions used have been well validated in the past(159).

The cross sectional nature of the data can limit the power of a study to identify all possible associations. This may be particularly likely in the setting of a secondary analysis. The point is highlighted by the finding that when GFR was analysed, a linear variable, positive associations were identified between renal impairment and diabetic end points. This reflects the increased power which is obtained from using a linear variable rather than the binary variables obtained from the majority of the data which is obtained in cross sectional studies.

6.6 Conclusions and recommendations

The results presented here add further information regarding the characterisation of renal impairment in the older diabetic person. The information which is currently available is extremely limited. This chapter showed that renal impairment appears to have associations with macrovascular disease, particularly cerebrovascular disease, in the older diabetic person. In general the associations demonstrated in this chapter were weaker than previous studies. The majority of the associations demonstrated here were between GFR and diabetic end points.

In general, the overall absence of associations seen in this chapter was surprising. Why should associations, between renal damage and diabetic end points, which are well established in younger people not be apparent with increasing age? It appears unlikely that they should. Therefore one has to suspect that the results generated from the MRC trial were biased. The most likely reason for this bias was the cross sectional nature of the study. The MRC trial was not designed to detect diabetic complications and was not powered to do so. It must therefore be suggested that further more appropriately designed studies are undertaken. The cross sectional nature of the study and the potential affect that that has had on the results generated in this chapter is expanded in chapter 9. In order to avoid repetition it was not discussed in detail here because it also affects some of the results from other chapters of this thesis.

Clearly there is room for further description of renal impairment among the older diabetic population to continue to characterise the condition.

Chapter 7 The relationship between admission to hospital and diabetes in the older person.

7.1 Summary of objectives

To assess the:

Association between diabetes and hospital admission in an elderly population.

7.2 Background

7.2.1 Introduction

If diabetes contributes to morbidity and mortality then health care use amongst people with diabetes is likely to be increased. This was previously observed in an older population in an assessment of the Medicare program utilisation(54). In the Medicare study, diabetes was established as an independent predictor of health care utilisation in 5138 community dwelling persons aged 71 years or older. The increased use of health care can manifest in several ways; an increased number of total admissions, an increased number of repeated admissions or an increased number of total days in hospital.

Social deprivation has been established as an independent risk factor for hospital admission for most chronic medical conditions, including diabetes, in all age groups(264;265). However information regarding other factors associated with admission to hospital in older age groups is sparse.

This thesis provided an opportunity to assess the total number of admissions to hospital, assess the number of repeat admissions, the length of stay of participants and some of the risk factors for admission to hospital in an older diabetic population.

7.2.2 Admission rates in diabetic populations

Analysis of the Veterans Administration diabetic cohort (n=33481) showed that since 1994 admission to hospital had increased in people aged over 75 years. They recorded total hospital discharges, in veterans with diabetes, on a yearly basis between 1994 and 1998, in all other age groups hospital admissions (recorded as discharges) were decreasing(266). The Veterans were nearly all men, predominantly white and had a mean age of 61.1 years.

7.2.3 Length of hospital stay

In 2005, a large hospital based audit, from Liverpool, showed that the average length of stay in hospital was increased for people with diabetes. The 113 patients, with predominantly type 2 diabetes and mean age 73 years, were in hospital for 19 days. This compared to 10 days for patients without diabetes(267). This figure is higher than Tayside, Scotland which used the DARTS database(268). In this study the average number of days which diabetic people spent in hospital was seven days. The Diabetes and Audit and Research in Tayside Scotland (DARTS) group studied 366849 people, of which 6871 had type 2 diabetes, with an average age of 67.6 years. The DARTS database is a well validated diabetes information system with 95% sensitivity for the identification of people with diabetes. A large retrospective cohort study of veterans in the US with type 2 diabetes demonstrated comparable results to the DARTS study. In the American study, the average length of stay was eight days(269).

7.2.4 Repeated hospital admission

A six year cohort study in the US showed that diabetes predisposed to repeated admission to hospital. Boult and colleagues studied the Medicare program and assessed 5876 people aged over 70 years(55). The authors found that eight factors emerged as risk factors for repeated admission; older age, male sex, poor self-rated general health, availability of an informal caregiver, having ever had coronary artery disease, a hospital admission within the previous year, more than six doctor visits, or diabetes. Jiang and colleagues showed that 55.2% of elderly people, with diabetes, have multiple stays in hospital as a percentage of total stays(270). This was in a large cohort of people (n=378226) aged over 65 years taken from the Healthcare Cost and Utilisation project database, representing five states in the U.S.

7.2.5 Factors associated with hospital admission in diabetic populations

Studies have established that access to health care is inversely proportional to admission rate in persons aged 18 to 64 years but not disease prevalence, physician admitting style or an individuals propensity to seek health care(271). Social deprivation has also been linked to increased hospital admission in diabetic populations. Positive correlations have been suggested between hospital admission and both being in receipt of disability living allowance and being a member of an unskilled socioeconomic group, for all diagnoses ($R=0.64$, $p<0.0001$ for disability allowance and $R=0.51$,

$p<0.0001$ for unskilled socioeconomic group (R=correlation coefficient))(264). A separate study, from 120 general practices in South London, confirmed these findings(265). The authors showed that deprivation, measured by the Jarman Index, was related to emergency admission to hospital ($R=0.46$, $p<0.001$). The study by Jiang, mentioned above, also showed that 29.9% of elderly people with diabetes and multiple admissions came from low income areas(270). When compared to the highest income areas, the odds ratio for admission was 1.03 (1.01-1.05 95% CI) $p<0.01$. Socioeconomic status was also found to be related to hospital admission in a study from Canada(272). A population based cohort of 605825 people with diabetes was analysed between the period 1992 and 1999. Socioeconomic data was calculated using neighbourhood level data derived from the 1996 Canadian Census. They found that individuals in the lowest quintile of income were more likely to be admitted to hospital when they attended the Emergency Department. In people of all ages the odds ratio for admission, lowest quintile vs highest quintile, was 1.20 (95% CI 1.14-1.26). A study of acute hospital admission in the Paisley and Renfrew area of Scotland found an association between increased BMI (BMI>30Kg/M^2) and hospital admission in people with abnormal glucose, odds ratio 3.19 (2.09-4.86 95% CI)(273). It should be noted that this study only included 103 people with abnormal glucose, who were aged between 45 and 64 years, from a total population of 15406.

7.3 Methods

7.3.1 Classification and identification of hospital admission rates, number of admissions and the average length of stay

Admission to hospital was collected for each trial participant for the two years immediately after they had completed the brief assessment. Nurses based within each participating general practice carried out six monthly notes searches on admission to hospital, based on the hospital discharge letter. The information recorded included date of admission, date of discharge and diagnosis. A patient was still classified as having been admitted to hospital even if they died during that admission. It should be noted that diagnosis was not considered further because this data was not considered to be accurate. There were some inaccuracies with the coding software used at the London School of Hygiene and Tropical Medicine to record the diagnosis, which made the recorded diagnosis unreliable. The software problems did not occur with the other information recorded regarding admission to hospital i.e. date of admission. Explanatory factors tested in the analysis were the same as for the analysis used in previous chapters of this thesis; sex, smoking history, excess alcohol intake, BMI, WHR, previous history of myocardial infarction or cerebrovascular accident, MMSE<=23 and quintiles of Carstairs index. Section 7.2.4, above, describes previously identified risk factors for repeated admission to hospital. Where comparable information was available from the MRC trial, the associations with hospital admission was assessed. These were the presence of an informal care giver and self rated health.

The questions regarding the presence of a care giver and self rated health were (see appendix 2);

- "Do you have a relative, neighbour or friend whom you can call on for help when required?" Yes or No.
- "Compared with other people of your own age would you say your health is generally: excellent, very good, good, fair or poor?"

The responses to the last question were regrouped into poor or otherwise. The justification for doing so was to simplify the outcome and increase the statistical power by making the outcome binary.

7.3.2 Analysis

Admissions for the non diabetic and the diabetic populations were described in terms of age and sex, allowing for the clustered studied design. The total number of days spent in hospital were calculated. Next the average number of admissions per diabetic subject was compared to the average number of admissions for the non diabetic subject. Repeated admission to hospital was then summarised for both populations. Next the average length of hospital stay was compared in days between the two groups. Poisson regression, comparing the rates of any admission between all diabetic individuals and non diabetic individuals, was then undertaken stratifying by five year age groups which calculated the rate of any admission for both populations. Every admission, single or multiple, was included. The Poisson model was tested at the 5% significance level using likelihood-ratio testing after any addition to the model of potential confounding factors or interaction terms.

Rate ratios were calculated for admission to hospital for the diabetic participants using Poisson regression. This allowed for the affect of associations to be tested, such as the affect of Carstairs index, the presence of a care giver or BMI. Each of these associations were adjusted for age group and sex.

7.4 Results

7.4.1 Description of the admissions to hospital for the MRC trial

There were a total of 80896 days spent in hospital for the entire population. The mean length of admission was 12.6 days. The range was from 0-427 days. The data was positively skewed (skewness=7.02), reflecting large numbers of people who weren't admitted to hospital at all (11170, 24.0%) and the small number of people who suffered a very long admission (72 (0.5%) people spent over 120 days in hospital). People admitted to hospital were more likely to be older ($p<0.001$) and male ($p<0.001$).

7.4.2 Rate of admission to hospital for the non diabetic and diabetic participants

Overall the rate of admission to hospital was higher for people with diabetes than people without diabetes. The rates also remained consistently higher for each age group when comparing the two populations. Similarly the rate of admission plateaus for both groups in the very elderly. Men showed higher rates of admission for both populations. Men and women with diabetes had higher rates of admission than those without diabetes. The rate ratios were consistently higher when the diabetic participants were compared to the diabetic participants, $p<0.01$ for each. The results are shown below in table 7.1.

Rate of Admission (1000/year, 95 %CI)		Participants without diabetes	Participants with diabetes	Rate Ratio*
Overall		187.90 (182.65-193.30)	246.45 (225.97-268.80)	1.31 (1.23-1.39)
Age group	75-79 years	161.50 (154.48-168.83)	224.32 (197.66-254.58)	1.39 (1.28-1.51)
	80-84 years	197.68 (188.20-207.63)	262.39 (225.37-305.51)	1.33 (1.20-1.47)
	85-89 years	237.10 (222.53-252.62)	289.00 (231.81-360.31)	1.22 (1.04-1.43)
	90 plus	219.33 (195.41-246.18)	267.46 (180.72-395.82)	1.22 (1.08-1.61)
Sex	Men	217.24 (208.05-226.84)	278.38 (246.38-314.33)	1.28 (1.18-1.39)
	Women	170.53 (164.25-177.05)	220.44 (194.78-249.47)	1.29 (1.18-1.41)

Table 7.1 Rates and rate ratios of admission to hospital; overall, age group and sex

*p<0.01 for each result, comparing diabetic with non diabetic participants

7.4.3 Average length of days spent in hospital per admissions to hospital for the non diabetic and diabetic participants

The non diabetic participants spent a total of 72564 days in hospital and the diabetic participants spent 8332 days in hospital. The average length of stay was 12.4 days and 13.9 days for the non diabetic and the diabetic participants respectively. The difference between the two was significant ($p<0.001$).

7.4.4 The number of hospital admissions for the non diabetic and diabetic participants

In the non diabetic population there were 3567 out of a population of 13918 (25.6%) people who had at least one admission to hospital. The majority (2331/13918, 16.7%) had just one admission. The range was between one and thirteen admissions. The average number of admissions per person was 1.58. Within the diabetic population 358/1177 (30.4%) people had one or more admission with 228/1177 (19.4%) having only one admission. The range was one to ten admissions. The average number of admissions per diabetic person was 1.64. In each case the results were significantly different ($p<0.001$, for each). The non diabetic population had a total of 5624 separate admissions to hospital and the diabetic population 558 separate admissions. In the non diabetic population multiple stays were 58.6% (as a percentage of total the stays) which was lower than the diabetic population whose multiple stays (as a percentage of total stays) was 67.2%. The results are shown in table 7.2.

	Participants without diabetes n=13918 (%)	Participants with diabetes n=1177 (%)
Number of (repeated) admissions		
0	10351 (74.42)	819 (69.60)
1	2331 (16.92)	223 (18.95)
2	775 (5.56)	85 (7.22)
3	254 (1.82)	28 (2.38)
4	117 (0.84)	12 (1.02)
5	50 (0.36)	4 (0.34)
6	28 (0.04)	3 (0.25)
7	8 (0.02)	1 (0.08)
8	2 (0.01)	1 (0.08)
9	0	0
10	1 (0.01)	1 (0.08)
11	0	0
12	0	0
13	1 (0.01)	0
Total number of separate admissions	5624	558

Table 7.2 Number of admissions; repeated and total

7.4.5 The factors which affected admission to hospital in older people with diabetes

Social deprivation (as measured by the Carstairs index) showed an association with increased admission in people from the lowest social economic group, (rate ratio, test for trend, p<0.01). Diabetic participants with MMSE <=23 (implying a high degree of cognitive impairment) did not show any change in the likelihood of being admitted to hospital. Equally alcohol had no affect on admission to hospital for either men or women. Smoking was associated with a trend toward admission to hospital when never, ex and current smokers were compared (test for trend, p<0.01). BMI did not show any relationship with admission to hospital. The absence of available help (someone to call in an emergency) was not associated with an increased rate ratio for admission to hospital. Poor self rated health and admission to hospital also showed no association. The results are shown in table 7.3.

		Number	Rate* (1000/year, 95 %CI)	Rate ratio (95% CI)	P value
Carstairs by quintile	1st (most deprived)	74	190.49 (151.68-239.24)	1.75 (1.64-1.86)	0.01
	2nd	131	235.01 (198.68-278.91)	1.34 (1.24-1.44)	test for
	3rd	114	226.23 (188.29-271.82)	1.19 (1.14-1.30)	trend
	4th	100	255.97 (210.41-311.40)	1.23 (1.12-1.32)	
	5th (least deprived)	70	334.61 (264.73-422.93)	1	(-)
MMSE	<=23**	106	281.13 (232.40-340.08)	1	(-)
	>23	426	231.90 (210.89-255.00)	0.87 (0.63-1.27)	0.42
Alcohol	0-21 units (men)	269	270.84 (240.17-305.42)	1	(-)
	>21 units (men)	5	312 (130.16-751.31)	1.62 (0.76-4.39)	0.18
	0-14 units (women)	256	220.61 (195.18-249.36)	(-)	(-)
	>14units (women)	2	^	(-)	(-)
Smoking	Never	163	196.27 (168.34-228.84)	1	(-)
	Ex-smoker	305	253.67 (226.74-283.80)	1.29 (1.18-1.40)	<0.01
	Current	63	359.21 (280.61-459.82)	1.83 (1.45-2.18)	trend
BMI	<18.5 Kg/m2	10	386.55 (207.98-718.42)	1	(-)
	18.5-25	178	286.27 (247.16-331.57)	0.74 (0.25-2.36)	0.09
	25-30	184	221.30 (191.53-255.70)	0.57 (0.22-1.86)	test for
	>30	104	190.99 (157.59-231.46)	0.49 (0.19-1.54)	trend
WHR	<0.90 (men)	72	343.97 (273.03-433.35)	1	(-)
	>0.90 (men)	183	250.61 (216.81-289.68)	0.72 (0.51-1.23	0.22
	<0.85 (women)	103	212.46 (175.15-257.72)	1	(-)
	>0.85 (women)	142	224.73 (190.64-264.90)	1.06 (0.90-1.25)	0.55
Help Availiable	Yes	474	236.71 (216.33-259.01)	1	(-)
	No	14	391.42 (231.82-660.90)	1.65 (0.96-2.34)	0.06
Self Rated Health	Better than poor	515	239.81 (219.97-261.45)	1	(-)
	Poor	14	304.30 (180.22-513.81)	1.27 (0.51-3.36)	0.99

Table 7.3 Rates and rate ratios for any admission to hospital in the diabetic population

*adjusted for age and sex, **indicates cognitive impairment, ^less than 3 events

7.5 Discussion

The results showed that people with diabetes had a higher rate of admission to hospital than people without diabetes. This was true for the diabetic population as a whole and when the diabetic population was assessed in terms of age group and sex. Each rate ratio was higher in the diabetic group, $p<0.01$ for each. Unsurprisingly, the absolute rates of admission increase with age. However, in both the non diabetic and the diabetic groups, the rates of admission to hospital plateau in those aged over 85 years. This could represent an unwillingness of these people to be admitted to hospital, possibly preferring to remain at home for treatment (or death) or a reluctance of healthcare providers to refer or admit these people to hospital.

The people with diabetes spent one and a half days longer in hospital than those without diabetes (13.9 days versus 12.4 days). The figure is less than the Liverpool study, where a younger population with diabetes (mean age 71 years) spent an average of 19 days in hospital per hospital admission(267). The DARTS group and the Veterans administration both showed a lower average length of hospital stay, seven and eight days respectively(268;269). There were some differences between the DARTS and the Veterans studies when they are compared to the MRC trial. The mean age in both studies was a lot lower than the MRC trial and the Veterans study contained very few women, factors which may account for the differences.

People with diabetes were more likely to suffer one or more admissions to hospital than people without diabetes (30.4% versus 25.6%). They also had a higher average number of admissions to hospital per person (1.64 in people with diabetes versus 1.58 in people without diabetes). These higher figures may reflect the increased burden of disease in the older diabetic person. The Healthcare Cost and Utilisation project database(270) previously found that 55.2% of diabetic people aged over 65 years had multiple stays in hospital which is lower than our older cohort for whom 67.2% had multiple hospital stays (as a percentage of total hospital stays).

When considering the factors which affected admission to hospital for the diabetic cohort only high Carstairs index and smoking demonstrated significantly raised rate ratios. The findings for the MRC trial for the Carstairs index were similar to previous studies which linked emergency admission to hospital to decreased social status(264;265;270;272). Current and ex smokers had an increased rate ratio for hospital admission, ($p<0.01$, test for trend), which presumably reflects the well established associations between smoking and disease. Available help has been previously shown to predispose to admission to hospital(55). The same study(55) found that poor self rated health increased admission to hospital, but neither of these two factors demonstrated an increased rate ratio for admission to hospital in the MRC trial. Increased BMI did not appear to increase hospital admissions. This result was different from the small Scottish study of younger people which found an association between admission to hospital and being obese (BMI>30 Kg/M^2)(273). Heavy drinkers, of either sex, or people with cognitive impairment, showed no differences for admission to hospital.

The diabetic population was analysed as a whole when the individual factors which affect hospital admission where considered, rather than separately by age group or sex. This ensured that numbers within each group studied remained large. By doing this statistical power remained high and the results more meaningful, albeit it a far broader group. This group (over 75 years and of either sex) is large and formed the first representative sample of the factors which affected admission to hospital in the older diabetic person.

There are of course other factors which influence hospital admission in the older diabetic person. These include both physical and social measures. For example, a three year prospective study in America found the Geriatric Depression score was an important independent risk factor for hospital admission(274). However, not every factor predictive of admission, including the Geriatric Depression score, was available in the MRC study. In the analysis of this study a large number of indices were used and their inclusion has been justified where possible.

The results of this chapter appear to confirm that diabetes contributes to hospital admission in every area; the rate of admission, the length of stay, total admissions and repeated admissions to hospital. It has also established some factors which increase the chances of hospital admission; low socio-economic status and smoking. The main criticism is the potential lack of power, particularly at the extremes of age. However, this study population is far older than those previously reported and provides new information regarding hospital admission in the elderly diabetic person.

Chapter 8 The relationship between diabetes and mortality in the older person

8.1 Summary of objectives

To compare the rate of death (all cause and cause specific; circulatory and renal) among older people with and without diabetes.

To assess the association between proteinuria, raised creatinine, glomerular filtration rate and mortality in the older diabetic subject.

8.2 Background

8.2.1 Introduction

Although it is likely that diabetes affects mortality in the older person, the evidence is sparse. Evidence first emerged of a detrimental affect of diabetes on life expectancy in the older person from two large studies from the Mayo clinic, now both over 30 years old(275;276). Using long term clinic data they followed diabetic people of all ages from 1939 onwards. In general both reports suggested that diabetes increased mortality in the older person, although some of the age and sex specific results differed between the two authors. The population demographics were different to modern populations and contained very few older people. In addition, mortality papers written before 1980, when the WHO markedly changed the diagnostic criteria of diabetes, were likely to classify people with impaired glucose tolerance (IGT), as having diabetes. The Bedford survey, a well known cohort study, showed that individuals with IGT, have raised mortality compared to the general population but lower mortality than people who have diabetes(277). Therefore the results of any mortality figures which were published before 1980, are likely to have been diluted by people with IGT and underestimate the true figure. Due to the age of the studies from the Mayo clinic (and therefore the different diagnostic criteria used today) and altered population demographics the findings reported in these papers may not be applicable today.

Since 1980, a number of studies have assessed mortality in diabetic older people and these are reviewed below. The affect of diabetes at the extremes of old age has not previously been assessed in the U.K, in a large population. The affect of diabetes on mortality in people aged over 90 years has not previously been published. In the older person the majority (but not all) of the mortality studies have concentrated on all cause mortality, although in younger populations all cause, cardiovascular and renal mortality are all raised. Whether cardiovascular and renal mortality are increased in the older person is less clear. Renal impairment (proteinuria, raised creatinine and decreasing GFR) is also an independent risk factor for all cause and cardiovascular mortality. The affect of renal impairment on mortality (of any cause) in the older diabetic person has rarely been assessed.

The associations between death (all cause, circulatory and renal) and diabetes and the affect of renal impairment and mortality in elderly people with diabetes were studied in this thesis to establish their affect.

8.2.2 All cause mortality in the older diabetic person

A comprehensive literature review, by Sinclair and colleagues(56), found that there was likely to be an association between diabetes and increased death rates in the older person. They reviewed papers relating to mortality from 1980 onwards and selected the most valid and useful. In total they included 20 papers in the review. The differences between the studies, including the different ages of the participants; different ethnic populations; the statistical methods used; the type of diabetes; different methods used to identify people with diabetes; and the length of follow up, were considered by the authors to preclude a meta analysis. The age of participants in the studies ranged from 55 years to greater than 85 years, although only two studies reported mortality figures for people aged over 80(278;279). The first of these from Finland, by Stengard and colleagues(278) included 82 men with diabetes (no women) and did not show a statistically significant increased rate of death in men aged 75 to 84 years (mortality ratio 1.8, 95% confidence interval 0.8-4.1) when compared to the non diabetic population. There was criticism of this study for the methods used to recruit diabetic participants. They identified trial participants using oral glucose tolerance tests (OGTT). Some of the OGTTs were performed after an inadequate period of fasting and some were conducted in the afternoon. This had the affect of overestimating the number of people defined as having diabetes and biased the results. The second study, by Croxson and colleagues(279), based in the UK (in a single town, Melton Mowbray) was the only study to provide hazard ratios of death for patients over the age of 85. The results of this study suggested that there was no increase in mortality in this age group, however, these results were based on only 6 participants aged over 85 years (hazard ratio 1.3 95% confidence interval 0.4-4.9). Unlike the Stengard study, a strength of this study was the appropriate use of OGTTs to identify trial subjects, therefore correctly identifying as many older diabetic people as possible. Of the remaining 18 articles reviewed, four provided mortality estimates for Caucasian populations aged over 75 years(280-283). Panzram and Zabel-Langhenning used a central diabetic registration database in Erfurt, Germany. They identified 50 women and 112 men aged between 75 and 79 years. They followed these people for 10 years and compared excess mortality to the general population. They found a mortality ratio of 1.04 for women and 0.96 for men(281). It was possible that the long period of follow up accounted for the lack of differences seen in this trial; if a cohort of people is followed up for long enough eventually the results will be the same, 100% death. Waugh *et al* studied type 1 and type 2 diabetic subjects in Dundee, Scotland and identified 201 subjects aged over 75 years. The authors calculated the relative risk of death to be 1.3 (95% CI, 0.9-1.9)(280). They also noted that a large number of the type 2 patients, especially the elderly, were under the care of their GP. This highlighted both the potential underestimation of the affect of diabetes on mortality in their results and difficulties of clinic based mortality studies in identifying all possible diabetic participants. There are also established differences in the care provided by hospital based and community based care, which forms another source of bias in hospital clinic based studies(284). The third study, this time from Aberdeen, Scotland, identified 1276 people with diabetes aged over 75, recruited from local GPs(282). They reported standardised mortality ratios (SMRs). They showed the SMR for men with diabetes was 0.81 (0.74-0.89) and 0.92 (0.84-1.01) for women. These results were liable to selection bias. The referral rates to the clinic were markedly different between General Practices, with some referral rates 96% and some referral rates not quoted. The extremely high referral rates and (potentially) low referral rates from different GPs implied that the diabetic clinic population may not have been representative of older diabetic people living in the community. The fourth study discussed in the review by Sinclair *et al*, which provided a mortality figure for a Caucasian population aged over 75 years was conducted by Walters and colleagues(283). They reported a SMR of 1.26 (1.08-1.45) for all cause mortality in a combined group of men and women aged over 75 years. They assessed a total population of 849 diabetic people, all aged over 45 years, but did not state how many were aged over 75 years.

The review by Sinclair and colleagues(56) provided an overview of articles published up to 1994. Since then there have been several large scale studies which addressed diabetic mortality in the older diabetic person. One of the most comparable to the MRC study was a study from Canada(161), which showed an increased risk of death amongst older diabetic people. Diabetes was identified using a self reported questionnaire. It included 9008 individuals aged 65 years and over. The risk of death was presented as an overall rate and not by age group or gender; relative risk 1.9, (95% CI 1.6-2.2). The Verona Diabetes Study showed that Standardised Mortality Ratios (SMR) were higher in people of all ages including those aged over 75 years. The SMRs for men and women aged over 75 years were 1.13 (1.00-1.28) and 1.32 (1.20-1.44) respectively. They demonstrated that SMRs declined with increasing age. For example, in the 45-54 year age group, the SMRs were 2.33 (1.38-3.69) for men and 3.43 (1.43-6.77) for women(285). The study also demonstrated that people with the most variation in fasting glucose results, measured using the coefficient of variation, also had a higher mortality. Another Italian study, by Bruno and colleagues, also showed decreasing SMRs as people with diabetes got older(58). They followed a cohort of 1967 people with type 2 diabetes. The average age of the group was 64.0+/-10.6 years and included people over the age of 80, although the paper did not state how many. For diabetic people aged 60-69 years, the SMR was 1.86 (1.52-2.25), for 70-79 years it was 1.37 (1.18-1.58) and for 80 plus years it was 1.12 (0.98-1.27). In 1997, a Danish study assessed the relative risk of death in 1323 Danes with diabetes, aged between 40 and 85 plus years(286). They showed relative risks of death to be 0.98 and 1.02 for men, aged 75-79 years (n=24) and 80-84 years (n=19). For women the relative risks were 1.24 and 1.19 for the same age groups (n=26 and n=25). The authors were unable to calculate relative risks for any participants aged over 85 years, due to "technical reasons" which they did not clarify. The small numbers of very elderly people should be noted and this was a clinic based study, thus possibly liable to selection bias (as discussed above). Roper and colleagues published overall death rates for men and women with diabetes aged over 80 years in the South Tees area of North East England(60). They showed that the death rate (per 1000 person years) for men aged over 80 years with diabetes was 155.56 (143.67-167.45) for the 131 men studied and 134.55 (127.70-141.41) for the 250 women studied. Compared to the non diabetic population the relative risks of death were 1.25 (1.09-1.43) and 1.09 (0.92-1.29) for men and women respectively. Once again the relative risk of death in this older age group was lower, for both men and women, than younger age groups. The South Tees study used a central diabetes register to identify diabetic people and consequently may have underestimated the true number of diabetic people in the community. A strength of the study was that nearly all the deaths were detected because all participants were registered for death at the Office for National Statistics. A large cohort study of 148519 older people with diabetes was analysed from the American Medicare system(57). The study compared the relative risk of death in Medicare beneficiaries with diabetes compared to non diabetic beneficiaries, in a predominantly (84.9%) white population. They found the relative risk of death to remain elevated, but once again declined with increasing age; 65-69 years, relative risk 2.59 (95% CI, 2.37-2.82), 70-74 years, 2.27 (2.19-2.35), 75-79 years, 2.11 (2.05-2.17), 80-84 years, 1.85 (1.80-1.90) and 85 plus years 1.46 (1.43-1.49). The primary limitation of this study was the use of claims data which does not identify all diabetic people. Identification of diabetic people from the Medicare system has previously been estimated to have a sensitivity of 63.4% and specificity of 98.8%. The use of claims data does not have the ability to identify undiagnosed diabetes within their population. Using the same cohort of participants, women with diabetes had a higher relative risk of death compared to men with diabetes even after adjustment for age, 1.34 (95% CI, 1.31-1.38)(287). Another large study, again using Medicare data, but with a different cohort of participants, assessed mortality rates for all cause mortality in people with diabetes(288). For the year 2001, they showed the mortality rate per year per 1000 Medicare beneficiaries to be 75.1 for people aged 75-79 years, 112.5 for ages 80-84 years and 202.2 for people aged over 85 years. The same limitations applied to this study as the previous one; namely the inability of claims data to identify all the people with diabetes from their population. A recent study published using the

DARTS database based in Tayside, Scotland(289)produced interesting up to date figures for mortality in the older diabetic person(290). They identified people who were diagnosed with diabetes at older age. They identified 3594 people with type 2 diabetes and 7188 age and sex matched comparators and assessed all cause and cardiovascular mortality over an average follow up period of 4.6 years. They identified the cause of death from death certificates (a noted limitation). In men, who were aged over 65 when they were diagnosed with diabetes, the relative risk of death was not increased regardless of the age of diagnosis. In women relative risk of death was increased for each age group of diagnosis. Women diagnosed at 65-74, 75-84 and over 85 years had relative risks of 1.47 (95% CI, 1.21-1.78), 1.15 (0.97-1.38) and 1.36 (1.06-1.73) respectively.

In summary, it appears that mortality rates in the older person, while remaining raised, decline with increasing age. In addition there is no overall consensus of the affect of gender and mortality in the older diabetic person. This summary is based on estimates primarily in "younger" older people, there are very few papers published in people aged over 85 years and none in people aged solely over 90 years.

8.2.3 Circulatory mortality

The predominant cause for excess mortality in younger people with diabetes is cardiovascular disease and this has been shown in many studies(44;60;162;291;292). For example, data from the First National Health and Nutrition Examination Survey (NHANES I) reported that "heart disease" was recorded on 69.5% of death certificates in people with diabetes(162). The importance of cardiovascular disease as a cause of death was further demonstrated in type 2 diabetic people from all over the world using the WHO multinational study of vascular disease in diabetes, (WHO MSVDD)(44). This study was conducted in 14 different centres and reported results from 10 centres. It assessed many diabetic vascular outcomes reporting separate results for type 1 and type 2 diabetic people aged between 35 and 54 years at recruitment. Morrish and colleagues showed that for the study population cardiovascular disease accounted for 52% of the deaths in the people with type 2 diabetes(292). The Verona diabetes study also stated that cardiovascular death remained raised in diabetic participants aged over 75 years but that the contribution of cardiovascular mortality was less in this age group when compared to the younger participants in their study(59). The authors suggested that cardiovascular mortality may have already caused the death of susceptible younger diabetic people and hence the decreasing affect of cardiovascular mortality was due to a survivor effect. They did not provide exact figures for different age groups for comparison. The South Tees group (whose paper was discussed above) provided cardiovascular cause specific mortality for older men and women(60). For males aged 60-79, the cardiovascular death rates (per 1000 person years) were 34.46 (31.47-37.46), relative risk 1.96 (1.72-2.23) and 80.50 (74.47-86.53), relative risk 1.39 (1.10-1.76) for men aged over 80 years. For the women aged 60-79 years the rates of death (per 1000 person years) were 34.25 (30.80-37.71), relative risk 3.24 (2.81-3.74) and for women aged over 80 years, 72.83 (67.62-78.04), relative risk 1.47 (1.22-1.77). The results by Tan and colleagues from the Diabetes and Audit and Research in Tayside

Scotland (DARTS) database failed to show a conclusive difference in cardiovascular mortality in their cohort of people who were diagnosed with diabetes at a later age(290). They showed that absolute numbers of cardiovascular deaths where higher in people with diabetes 49.4% vs 45.2%, but the adjusted relative risk of cardiovascular death was 1.01 (0.93-1.10).

Circulatory disease has been established as a major cause of death in people with diabetes. It has also been suggested, that in a similar manner to all cause mortality, mortality rates remain raised but decrease with advancing age. A potential explanation for the decreasing affect is the survivor effect, with susceptible individuals succumbing to circulatory death before they reach old age.

8.2.4 Renal mortality

The WHO MSVDD showed that renal disease accounted for 8% of deaths in men and 14% for women in their worldwide population with type 2 diabetes(292). This was not, however, an elderly population. The oldest person in this population was aged 54 years at recruitment, and the cohort followed for an average of 8.4 years(44). There was no other evidence available describing the affect of diabetes on renal mortality in the older diabetic person.

In addition to their contribution to end stage renal disease (ESRD), poor renal function and proteinuria have both been established as independent risk factors for both all cause(60) and cardiovascular mortality(65). In younger populations with type 2 diabetes and ESRD the five year survival is worse than non diabetic ESRD patients. Five year survival has been reported to be as low as 29%(293). The first study which identified the link between microalbuminuria, clinical proteinuria and death was conducted by Morgensen in 1984(294). Since then studies have increased in size and range, the results of which can be illustrated by a recent large Italian study (n=3892, mean age 69.7 years). This study, based in Turin, recruited type 2 diabetic people and confirmed that renal impairment (micro and macroalbuminuria and impaired renal function) all contributed to increased hazard ratios for both all cause and cardiovascular death. While the trial did include people aged over 75 years no hazard ratios were presented specifically for these age groups(295). In the U.K. a five year retrospective study of type 2 diabetes in Manchester showed that proteinuria was associated with all cause and cardiovascular death. In patients with an average age of 58.2 years mortality was directly related to increasing proteinuria. For each log unit increase in proteinuria a 36% excess risk of mortality was observed. The hazard ratio for cardiovascular disease in patients with nephropathy (proteinuria or raised creatinine) was 5.56 (1.62-19.06) p=0.006(65). Globally, Fuller *et al*(291), used the WHO MSVDD study to demonstrate that proteinuria was an independent risk factor for cardiovascular death. The study demonstrated that in type 2 diabetes the relative risk of cardiovascular death continued to increase for both men and women with diabetes as proteinuria increased from no proteinuria, to light proteinuria and to heavy proteinuria. The South Tees study was the only study published which assessed the affect of altered renal function and death in the older diabetic person. They showed that creatinine above 150 μmol/l markedly increased the death rate in type 2 diabetic people aged over 80 years compared to diabetic people with creatinine less than 150 μmol/l of the same age, relative rate 1.92 (1.60-2.31). The 30 people with raised creatinine had an all cause death rate (per 1000 person years) of 260.90 (95% CI, 202.35-319.46), relative rate 1.92 (1.60-2.31)(60).

Worsening GFR, before the onset of ESRD, has been linked to death and cardiovascular disease(296). This large survey used the Kaiser Permanente Renal Registry to identify people with renal insufficiency, but not ESRD. They demonstrated that both the risk of death and cardiovascular disease increased with decreasing GFR.

There is very little evidence available for renal death, diabetes and the older person but it is likely that diabetes increases the renal death rate in older people. Proteinuria, renal impairment and worsening GFR have been established as independent predictors of death in older diabetic people. However, this thesis provided a larger population on which to test those findings.

8.3 Methods

8.3.1 Identification of participants in the MRC trial who died

All participants were registered with the Office for National Statistics (ONS) who provided information on date and coded cause of death (including any cause mentioned on the death certificate and the underlying cause of death). The ONS used the International Classification of Diseases, 9th revision (ICD-9) for deaths reported up to September 2002 (86% of the deaths analysed for this thesis) and the 10th revision (ICD-10) after that date. Analyses were based on deaths for all cause mortality, circulatory mortality and renal mortality. The cause of death used in the MRC trial was the cause of death identified by the ONS, as the underlying cause of death on the death certificate. Underlying causes coded as circulatory used codes 390-459 in ICD9 and I1-I99 in ICD10, and for renal disease used codes 580-589 in ICD 9 and codes N00-N19 in ICD10. Changes in coding between ICD9 and ICD10 did not affect the broad classifications used in this thesis.

A previous estimate from English and Welsh death certificates suggested that diabetes was recorded (either immediate cause of death or any mention of diabetes) in 67% of people who have diabetes(297) These findings were found to have worsened over recent years. The analysis of the death certificates of participants in the UKPDS was published (on-line) in 2005. There were 981 deaths in their solely diabetic population and diabetes (any record) was found on only 419 (42%) of the death certificates(298). In the MRC trial diabetes was recorded on some certificates, however this was likely to underestimate the true figure by at least 30%, but the recent

UKPDS paper suggested a lot more. Therefore diabetes as a cause of death was not considered further.

Practices and patients were recruited during four years (1995 to end 1998), mortality analyses were based on the first five years of follow-up for every eligible patient from baseline to ensure that all individuals had potentially the same length of follow-up. Information regarding death was complete up to the end of October 2003. All trial participants who were analysed in this thesis either died within five years or completed five years of follow up.

8.3.2 Analysis

There were 51787 (98.8%) participants out of 52401 who entered the original trial, regardless of their responder status, who were registered for mortality flagging. Death records were not complete because some of the records were deemed unreliable and some of the trial participants had emigrated.

In order to make comparisons between the responders and non responders, death rates, hazard ratios and Kaplan-Meier survival plots were generated. Death, age and sex were the only variables which were available for the non responders and therefore these results were presented after adjustment of age group and sex. It was not possible to assess the affect of other factors on non responding participants.

Rates of death were calculated for participants with and without diabetes. These were calculated per 1000 persons per year. All cause mortality, mortality within each age group and by sex are given for all cause, circulatory and renal mortality. All cause and circulatory death rates within age group and by sex were also calculated for diabetic people with and without proteinuria and raised creatinine. Circulatory mortality did not include heart failure, which is coded differently in the ICD classification.

Cox proportional hazards models were constructed allowing for clustering by practice. All the possible potential explanatory factors discussed in this thesis were incorporated in the model. These were age group, sex, smoking status, BMI, WHR, previous history of myocardial infarction, previous history of cerebrovascular disease, proteinuria, raised creatinine, systolic blood pressure >130 mmHg, diastolic blood pressure >80 mmHg, any one to call for help, poor self rated health, quintile of Carstairs index, MMSE<=23 and high alcohol intake. After the addition of each variable to the model visual inspection of the proportional hazard ratio was undertaken to ensure that it was maintained. The proportional hazards ratio was also tested. Any changes in the hazard ratio were observed. In order to maintain the most parsimonious model possible variables were only left in the final model if the hazard ratio for death, changed by five percent and the proportional hazard testing was not significant, p>0.05, (significance indicates a departure from proportionality).

Kaplin-Meier survival graphs were created for all cause mortality for the five year period of follow up. For all cause mortality they are presented for trial non responders compared with responders, diabetic participants versus non diabetic participants, diabetic participants with and without proteinuria and diabetic participants with and without raised creatinine. Survival graphs are also presented for diabetic and non diabetic subjects for circulatory and renal mortality. Circulatory mortality survival graphs are also presented for diabetic subjects with and without proteinuria and raised creatinine. All the Kaplan-Meier survival graphs were adjusted for any variables included in the final Cox model.

Chapters 3 and 6 of this thesis raised interesting questions about GFR calculated using the MDRD modified equation. Chapter 3 suggested that despite higher mean creatinine in diabetic people than non diabetic people, mean GFR was not different between people with and without diabetes. Chapter 6 showed worsening GFR was a good predictor of macrovascular disease in people with diabetes. In order to further test the validity of GFR in the older person a hazard ratio for death for decreased GFR was calculated. GFR was assessed for each unit change in GFR and for GFR above and below 60 ml/min per 1.73 m^2. This was performed in the non and the diabetic populations for all cause death, circulatory and renal death.

8.4 Results

8.4.1 The relationship between questionnaire response and mortality

There were 21140 people randomised to the universal arm of the MRC trial, of whom 15095 (71.4%) responded to the detailed assessment. There were 2842 (47.0%) deaths out of a total of 6315 non responders and 5072 (33.6%) deaths in the 15095 people who responded. The rate of death per 1000 persons per year was 119.4 (95%CI, 109.7-130.3) in the non responding group and 80.3 (76.3-84.5) in those who responded. The unadjusted hazard ratio for death in the non responding group compared to the responding group was 1.49 (1.38-1.62), $p<0.001$. There was no evidence of departure from the proportional hazards assumption, $p=0.26$. The Kaplan-Meier survival plot is shown below in figure 8.1. Apart from death, the MRC trial only contained information regarding age and sex for the non responding participants. After adjustment for age and sex the hazard ratio for death comparing the non responding group versus the responding group was 1.44 (1.33-1.56), $p<0.001$.

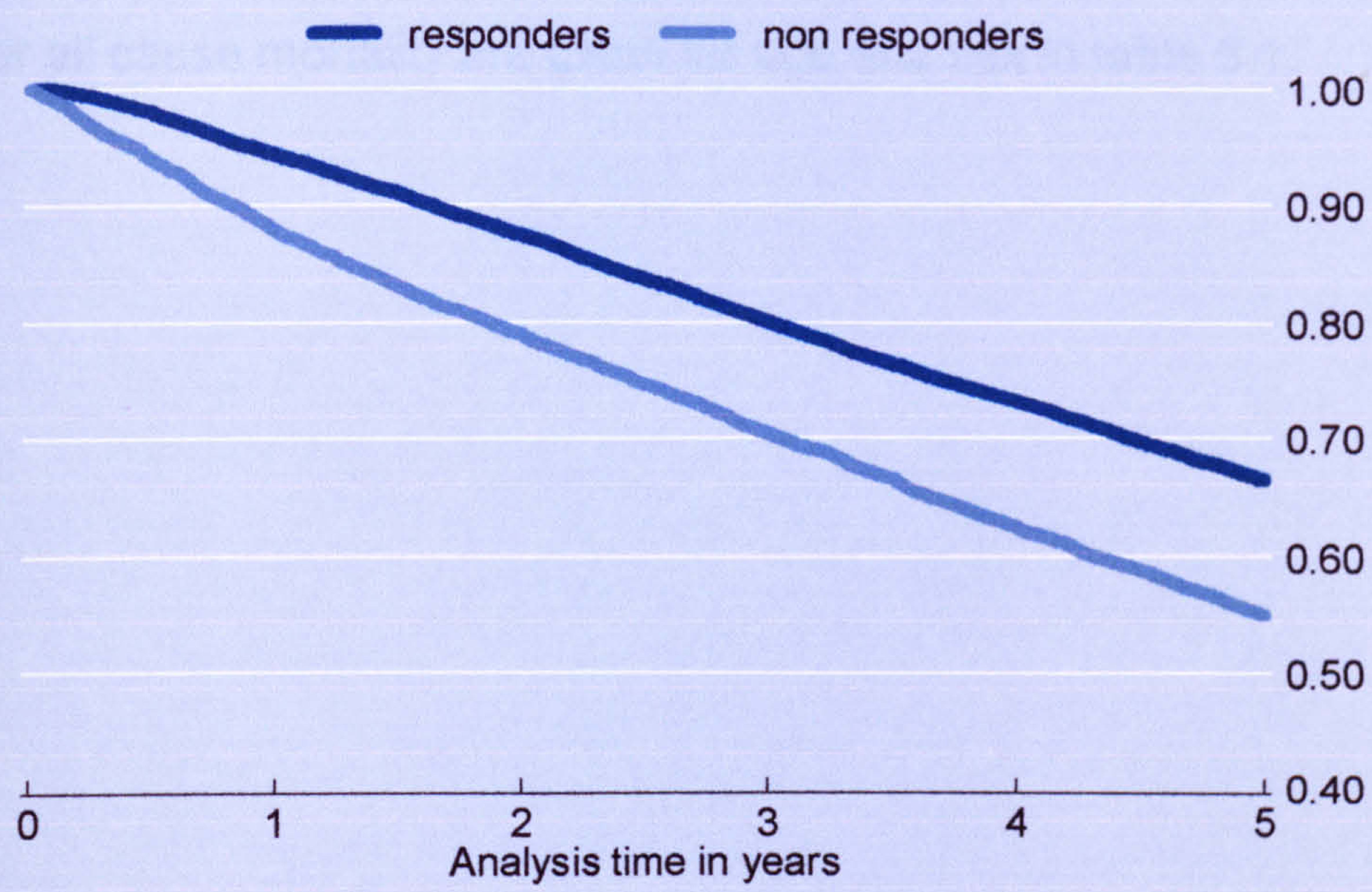


Figure 8.1. Kaplan-Meier survival estimates by responder status

8.4.2 Total numbers of deaths and death rates for diabetic participants in the MRC trial

The overall numbers and rate of death for the whole cohort were given above in section 8.4.1. For the responding participants; in the 75-79 years age group there were 1612 (22.89%) deaths out of a total population of 7042 in the five year follow up period. In the 80-84 year group 1640 (34.47%) deaths out of 4758 people, in the 85-89 years group 1236 (50.63%) deaths out of 2441 people and in the 90 plus age group there were 584 (68.38%) deaths out of 854 people. In the diabetic population there were 517 deaths (43.93%) out of a total diabetic population of 1177. For the diabetic population the total numbers of deaths were; 200 (34.19%) deaths from the 585 diabetic people aged 75-79 years, 161 deaths (44.23%) of the 364 people aged 80-84 years with diabetes, 110 deaths (65.87%) of the 167 people with diabetes aged 85-89 years and 46 deaths (74.41%) of the 61 people aged over 90 years with diabetes. The rates of death for all cause mortality are given for age and sex in table 8.1.

		Participants without diabetes (**n=13918**)		Participants with diabetes (**n=1177**)	
		Total person years of follow up **(number of deaths)**	Rate of death (1000 persons/year, 95 %CI)	Total person years of follow up **(number of deaths)**	Rate of death (1000 persons/year, 95 %CI)
All cause mortality					
Overall		58622 **(4555)**	77.7 (73.9-81.7)	4548 **(517)**	113.7 (103.4-125.2)
Age group	75-79 years	29032 **(1412)**	48.6 (45.0-52.6)	2449 **(200)**	81.8 (70.2-95.9)
Men and women	80-84 years	18462 **(1479)**	80.1 (75.4-85.1)	1388 **(161)**	116.0 (100.2-134.7)
	85-89 years	8621 **(1126)**	130.6 (121.9-139.9)	545 **(110)**	201.9 (168.8-243.1)
	90 plus	2508 **(538)**	214.5 (197.1-233.6)	172 **(46)**	268.2 (220.4-327.2)
Sex	Men	21450 **(1940)**	90.9 (85.2-97.0)	2042 **(264)**	129.3 (113.6-147.6)
All ages	Women	37273 **(2615)**	70.2 (66.0-74.7)	2506 **(253)**	101.0 (88.7-115.3)
Age group	75-79 years	11728 **(744)**	63.4 (57.1-70.7)	1257 **(123)**	97.9 (81.5-118.4)
Men only	80-84 years	6421 **(640)**	99.7 (92.1-108.1)	541**(78)**	144.0 (114.8-182.0)
	85-89 years	2703 **(418)**	154.7 (136.8-175.0)	201 **(49)**	244.4 (186.8-321.8)
	90 plus	498 **(138)**	277.1 (237.0-324-.0)	42 **(14)**	327.5 (200.0-538.4)
Age group	75-79 years	17304 **(668)**	38.6 (35.3-42.3)	1187 **(77)**	64.9 (51.6-82.6)
Women only	80-84 years	12041 **(839)**	69.7 (64.3-75.6)	846 **(83)**	98.1 (78.8-122.7)
	85-89 years	5918 **(708)**	119.6 (112.0-127.7)	344 **(61)**	117.2 (140.3-223.7)
	90 plus	2010 **(400)**	199.0 (179.6-220.9)	128 **(32)**	248.5 (187.4-332.1)

Table 8.1 Death rates, person years and numbers of deaths for all cause mortality for the diabetic and non diabetic participants

In the whole population there were 2720 (53.6%) deaths for which circulatory disease was listed as the underlying cause of death, out of a total of 5072 deaths. There were 285 (55.1%) deaths in the diabetic participants whose underlying cause of death was listed as circulatory disease out of a total of 517 deaths. The overall rate and rates by sex and age group are shown for circulatory mortality in table 8.2.

		Participants without diabetes **(n=13918)**		Participants with diabetes **(n=1177)**	
		Total person years of follow up **(number of deaths)**	Rate of death (1000 persons/year, 95 %CI)	Total person years of follow up **(number of deaths)**	Rate of death (1000 persons/year, 95 %CI)
Circulatory mortality					
Overall		58622 **(2435)**	41.5 (38.5-44.9)	4548 **(285)**	62.7 (55.7-70.8)
Age group	75-79 years	29032 **(794)**	27.4 (24.5-30.6)	2444 **(120)**	49.3 (41.3-58.8)
Men and women	80-84 years	18462 **(852)**	46.1 (42.1-50.7)	1388 **(89)**	64.1 (53.6-77.2)
	85-89 years	8621 **(573)**	66.5 (59.5-74.3)	545 **(53)**	97.3 (80.7-118.4)
	90 plus	2508 **(216)**	86.1 (75.7-98.3)	172 **(23)**	134.1 (91.3-205.2)
Sex	Men	21350 **(1022)**	47.9 (43.9-52.3)	2042 **(124)**	60.7 (50.6-73.6)
All ages	Women	37273 **(1413)**	37.9 (34.8-41.3)	2506 **(161)**	64.2 (55.3-75.0)
Age group	75-79 years	11728 **(404)**	34.4 (30.2-39.5)	1257 **(68)**	54.1 (43.2-68.6)
Men only	80-84 years	6421 **(372)**	57.9 (51.9-65.0)	542 **(33)**	60.9 (45.6-83.0)
	85-89 years	2703 **(190)**	70.3 (58.4-84.9)	201 **(18)**	89.8 (63.7-129.7)
	90 plus	498 **(56)**	112.4 (86.4-149.3)	42 **(5)**	117.0 (51.7-296.9)
Age group	75-79 years	17304 **(390)**	22.5 (19.7-26.0)	1187 **(52)**	43.8 (34.4-56.9)
Women only	80-84 years	12041 **(480)**	38.9 (35.5-44.9)	846 **(56)**	66.2 (51.6-85.5)
	85-89 years	5918 **(383)**	64.7 (57.6-72.9)	344 **(35)**	101.7 (79.6-131.1)
	90 plus	2010 **(160)**	79.6 (67.1-94.9)	128 **(18)**	139.8 (80.2-262.4)

Table 8.2 Death rates, person years and numbers of deaths for circulatory mortality for the diabetic and non diabetic participants

Renal disease was listed as the underlying cause of death in 109 (2.1%) of all 5072 deaths. This figure was 17 (2.9%) in the diabetic population, which had 517 deaths. The overall rate and rates by sex and age group are shown for renal mortality in table 8.3. Please note that some of the age and sex specific groups contained less than three deaths which made statistical analysis unreliable due to the small numbers.

		Participants without diabetes **(n=13918)**		Participants with diabetes **(n=1177)**	
		Total person years of follow up **(number of deaths)**	Rate of death (1000 persons/year, 95 %CI)	Total person years of follow up **(number of deaths)**	Rate of death (1000 persons/year, 95 %CI)
Renal mortality					
Overall		58622 **(92)**	1.6 (1.3-2.0)	4548 **(17)**	3.7 (2.4-6.0)
Age group	75-79 years	29032 **(22)**	0.8 (0.5-1.2)	2444 **(7)**	2.9 (1.4-6.5)
Men and women	80-84 years	1517 **(28)**	1.5 (1.0-2.3)	1388 **(5)**	3.6 (1.3-13.7)
	85-89 years	2784 **(24)**	2.8 (1.9-4.1)	545 **(5)**	9.2 (4.0-25.7)
	90 plus	2508 **(18)**	7.2 (4.5-12.4)	(-)*	(-)*
Sex	Men	21350 **(42)**	2.0 (1.4-2.8)	2042 **(6)**	2.9 (1.2-8.9)
All ages	Women	37273 **(50)**	1.3 (1.0-1.8)	2506 **(11)**	4.4 (2.6-8.3)
Age group	75-79 years	11728 **(17)**	1.4 (0.9-2.4)	1257 **(3)**	2.4 (0.8-11.0)
Men only	80-84 years	6421 **(7)**	1.1 (0.5-2.9)	(-)*	(-)*
	85-89 years	2703 **(12)**	2.7 (2.5-8.7)	(-)*	(-)*
	90 plus	498 **(6)**	12.0 (6.1-27.9)	(-)*	(-)*
Age group	75-79 years	17304 **(5)**	0.3 (0.1-0.8)	1187 **(4)**	3.4 (1.3-11.5)
Women only	80-84 years	12041 **(21)**	1.7 (1.1-2.9)	846 **(3)**	3.5 (1.2-15.3)
	85-89 years	5918 **(12)**	2.0 (1.2-3.7)	344 **(4)**	11.6 (4.4-39.4)
	90 plus	2010 **(12)**	6.0 (3.6-10.7)	(-)*	(-)*

Table 8.3 Death rates, person years and numbers of deaths for renal mortality for the diabetic and non diabetic participants

*each group had less than 3 deaths

Rates are also presented for all cause mortality for diabetic participants with and diabetic participants without proteinuria and raised creatinine. The rates are presented in terms of the overall rate and by age group and gender. The results are shown in tables 8.4 and 8.5.

		Participants without proteinuria **(n=909)**		Participants with proteinuria **(n=188)**	
		Total person years of follow up **(number of deaths)**	Rate of death (1000 persons/year, 95 %CI)	Total person years of follow up **(number of deaths)**	Rate of death (1000 persons/year, 95 %CI)
All cause mortality					
Overall		3594 **(366)**	101.9 (91.4-113.7)	676 **(105)**	155.3 (133.1-181.5)
Age group	75-79 years	1961 **(141)**	71.9 (60.1-86.6)	361 **(44)**	121.9 (96.6-154.8)
Men and women	80-84 years	1098 **(117)**	106.6 (88.1-129.7)	204 **(34)**	116.5 (120.9-230.7)
	85-89 years	406 **(76)**	187.0 (154.5-226.2)	96 (21)	216.7 (137.8-359.3)
	90 plus	128 **(32)**	249.9 (189.7-329.8)	14 **(6)**	430.9 (238.6-679.1)
Sex	Men	1614 **(196)**	121.4 (104.7-141.6)	328 **(51)**	155.3 (127.6-188.5)
All ages	Women	1979 **(170)**	85.9 (71.8-103.3)	347 **(54)**	155.3 (124.6-195.0)
Age group	75-79 years	980 **(89)**	90.8 (73.4-113.8)	206 **(27)**	131.4 (102.9-168.7)
Men only	80-84 years	444 **(58)**	130.8 (101.2-171.3)	88 **(15)**	169.4 (116.6-244.9)
	85-89 years	159 **(38)**	239.8 (176.7-326.8)	30 **(7)**	235.7 (132.3-450.9)
	90 plus	32 **(11)**	339.9 (182.1-638.5)	(-)*	(-)*
Age group	75-79 years	981 **(52)**	53.0 (39.4-72.9)	156 **(17)**	109.3 (73.2-166.5)
Women only	80-84 years	654 **(59)**	90.2 (67.7-121.6)	116 **(19)**	164.2 (104.3-268.9)
	85-89 years	248 **(38)**	153.3 (119.4-195.9)	67 **(14)**	208.3 (126.2-362.3)
	90 plus	95 **(21)**	219.5 (148.0-327.6)	9 **(4)**	433.0 (236.7-728.7)

Table 8.4 Death rates, person years and numbers of deaths for all cause mortality for the diabetic participants with and without proteinuria *each group had less than 3 deaths

		Participants without raised creatinine **(n=806)**		Participants with raised creatinine **(n=236)**	
		Total person years of follow up **(number of deaths)**	Rate of death (1000 persons/year, 95 %CI)	Total person years of follow up **(number of deaths)**	Rate of death (1000 persons/year, 95 %CI)
All cause mortality					
Overall		3245 **(302)**	93.1 (84.2-103.0)	821 **(135)**	164.5 (134.3-201.7)
Age group	75-79 years	1836 **(121)**	65.9 (55.8-78.2)	377 **(48)**	127.5 (91.2-178.7)
Men and women	80-84 years	952 **(96)**	100.9 (84.4-121.0)	276 **(41)**	148.6 (105.9-212.2)
	85-89 years	332 **(56)**	168.6 (132.7-214.2)	140 **(37)**	265.0 (198.0-356.0)
	90 plus	125 **(29)**	232.3 (166.5-326.5)	29 **(9)**	315.6 (175.2-545.0)
Sex	Men	1338 **(147)**	109.8 (93.3-129.8)	536 **(87)**	162.4 (126.6-208.2)
All ages	Women	1907 **(155)**	81.3 (70.9-93.4)	285 **(48)**	168.5 (125.9-227.8)
Age group	75-79 years	868 **(73)**	84.1 (66.7-107.3)	290 **(35)**	120.7 (83.2-174.7)
Men only	80-84 years	339 **(43)**	126.8 (96.2-169.6)	157 **(24)**	153.3 (102.9-234.3)
	85-89 years	94 **(21)**	223.9 (150.4-334.3)	84 **(24)**	286.1 (203.4-402.9)
	90 plus	38 **(10)**	226.3 (148.9-480.50	5 **(4)**	770.6 (315.2-1605.0)
Age group	75-79 years	969 **(48)**	49.6 (37.8-66.1)	87 **(13)**	150.2 (81.7-290.9)
Women only	80-84 years	312 **(53)**	86.6 (67.9-110.6)	119 **(17)**	142.4 (77.5-279.7)
	85-89 years	238 **(35)**	146.9 (108.7-197.5)	56 **(13)**	233.4 (133.4-421.9)
	90 plus	87 **(19)**	217.7 (139.5-346.8)	23 **(5)**	214.4 (97.8-480.8)

Table 8.5 Death rates, person years and numbers of deaths for all cause mortality for the diabetic participants with and without raised creatinine

Finally rates are presented for all circulatory mortality for diabetic participants with and without proteinuria and raised creatinine. The rates are presented in terms of the overall rate and by age group and gender. The results are shown in tables 8.6-7.

Rates of renal mortality in relation to proteinuria and raised creatinine were not calculated for specific age groups and gender. This was because of the low number of diabetic people who suffered from renal mortality made the majority of the rates meaningless, due to the low numbers within each group, when specific age group and sex analysis was attempted. However, overall rates and hazard ratios for men and women of all ages were calculated (the results of which are shown in section 8.4.9).

		Participants without proteinuria **(n=909)**		Participants with proteinuria **(n=188)**	
		Total person years of follow up **(number of deaths)**	Rate of death (1000 persons/year, 95 %CI)	Total person years of follow up **(number of deaths)**	Rate of death (1000 persons/year, 95 %CI)
Circulatory mortality					
Overall		3594 **(208)**	57.9 (50.6-66.6)	676 **(54)**	79.9 (64.6-99.3)
Age group	75-79 years	1961 **(89)**	45.4 (37.2-55.9)	361 **(22)**	60.9 (45.9-82.5)
Men and women	80-84 years	1098 **(63)**	57.4 (46.5-71.4)	1388 **(5)**	102.8 (69.5-151.1)
	85-89 years	406 **(39)**	96.0 (75.8-122.8)	97 **(8)**	82.6 (43.9-179.3)
	90 plus	128 **(17)**	132.8 (84.2-219.9)	14 **(3)**	215.4 (91.9-502.5)
Sex	Men	1614 **(96)**	59.5 (48.9-73.3)	328 **(20)**	60.9 (41.8-91.0)
All ages	Women	1979 **(112)**	56.6 (46.4-69.7)	348 **(34)**	97.8 (73.3-132.7)
Age group	75-79 years	980 **(52)**	53.1 (41.2-69.5)	206 **(11)**	53.5(34.8-85.7)
Men only	80-84 years	444 **(25)**	56.4 (41.7-78.5)	89 **(6)**	67.8 (35.1-139.5)
	85-89 years	159 **(15)**	94.7 (64.6-142.0)	(-)*	(-)*
	90 plus	32 **(4)**	123.6 (47.3-377.1)	(-)*	(-)*
Age group	75-79 years	981 **(37)**	37.7 (27.9-52.4)	156 **(11)**	70.7 (42.9-123.6)
Women only	80-84 years	654 **(38)**	58.1 (42.3-80.8)	116 **(15)**	129.6 (83.5-200.6)
	85-89 years	248 **(24)**	96.8 (72.0-132.0)	67 **(6)**	89.3 (39.0-263.3)
	90 plus	96 **(13)**	135.9 (72.8-274.4)	(-)*	(-)*

Table 8.6 Death rates, person years and numbers of deaths for circulatory mortality for the diabetic participants with and without proteinuria *each group had less than 3 deaths

		Participants without raised creatinine **(n=806)**		Participants with raised creatinine **(n=236)**	
Rate of death (1000 persons/year, 95 %CI)		Total person years of follow up **(number of deaths)**		Total person years of follow up **(number of deaths)**	
Circulatory mortality					
Overall		3245 **(164)**	50.5 (44.5-57.7)	821 **(70)**	85.3 (62.7-117.2)
Age group	75-79 years	1836 **(72)**	39.2 (31.7-49.1)	377 **(27)**	71.7 (44.9-116.5)
Men and women	80-84 years	952 **(55)**	57.8 (45.9-73.6)	276 **(18)**	65.2 (38.0-120.5)
	85-89 years	332 **(25)**	75.3 (55.0-105.3)	140 **(20)**	143.3 (98.7-210.8)
	90 plus	129 **(12)**	96.1 (59.0-168.6)	29 **(5)**	175.3 (89.3-364.8)
Sex	Men	1338 **(65)**	48.6 (38.6-62.1)	536 **(40)**	74.7 (49.2-115.4)
All ages	Women	1907 **(99)**	51.9 (44.2-61.4)	285 **(30)**	105.3 (70.9-159.3)
Age group	75-79 years	868 **(36)**	41.5 (30.0-59.0)	290 **(21)**	72.4 (43.0-123.2)
Men only	80-84 years	339 **(20)**	59.0 (41.1-87.4)	157 **(6)**	38.3 (18.7-89.1)
	85-89 years	94 **(6)**	64.0 (25.8-193.4)	84 **(11)**	131.1 (76.6-231.6)
	90 plus	(-)*	(-)*	(-)*	(-)*
Age group	75-79 years	969 **(36)**	37.2 (28.6-49.4)	87 **(6)**	69.3 (29.1-199.5)
Women only	80-84 years	612 **(35)**	57.2 (41.4-80.1)	119 **(12)**	100.5 (52.1-212.0)
	85-89 years	238 **(19)**	79.7 (54.5-119.6)	56 **(9)**	161.6 (92.7-298.2)
	90 plus	87 **(9)**	130.1 (50.0-242.2)	(-)*	(-)*

Table 8.7 Death rates, person years and numbers of deaths for circulatory mortality for the diabetic participants with and without raised creatinine *each group had less than 3 deaths

8.4.3 Hazard ratios for all cause mortality for people with diabetes compared to those without diabetes

The final adjusted hazard ratio for death due to diabetes for men and women aged over 75 years was 1.50 (95% CI, 1.38-1.65). The crude unadjusted hazard ratio for death from diabetes was 1.48 (95% CI, 1.35-1.61). The Cox proportional hazard model (and hazard ratio) is shown for every variable tested in table 8.8. When every possible variable was included in the model the adjusted hazard ratio was 1.42 (95%CI, 1.27-1.59). However, this was not a parsimonious model and does not conform to the predetermined modelling strategy; significance within the model and large alteration of the hazard ratio. The table shows that systolic blood pressure over 130 mmHg, diastolic blood pressure over 80 mmHg, having no one to call for help, difficulty making ends meet, living alone and high alcohol intake (men or women), waist hip ratio above 0.9 (men only) were not significant in the model containing every variable. They were excluded from the model and not used further.

		Hazard Ratio, (95% CI)	P value
Crude HR diabetes		1.48 (1.35-1.61)	(-)
Adjusted HR diabetes		1.42 (1.27-1.59)	<0.001
Variable*			
Age group (years)	75-79	1	(-)
	80-84	1.56 (1.44-1.70)	<0.001
	85-89	2.46 (2.21-2.76)	<0.001
	90 plus	4.60 (3.98-5.33)	<0.001
Sex	Male	1	(-)
	Female	0.74 (0.69-0.80)	<0.001
Smoking	Never	1	(-)
	Ex-smokers	1.20 (1.11-1.30)	<0.001
	Current	1.67 (1.46-1.91)	<0.001
BMI	<18.5 Kg/m2	1	(-)
	18.5-25	0.57 (0.47-0.69)	<0.001
	25-30	0.44 (0.36-0.52)	<0.001
	>30	0.48 (0.39-0.58)	<0.001
WHR	Men (<0.90)	0.90 (0.80-1.01)	0.08
	Women (<0.85)	1.25 (1.16-1.36)	<0.001
Previous MI		1.51 (1.36-1.66)	<0.001
Previous CVA		1.40 (1.21-1.62)	<0.001
Proteinuria		1.35 (1.20-1.53)	<0.001
Raised Creatinine		1.53 (1.38-1.69)	<0.001
Systolic blood pressure >130 mmHg		0.97 (0.88-1.07)	0.51
Diastolic blood pressure >80 mmHg		1.01 (0.94-1.09)	0.75
Anyone to call for help		1.10 (0.87-1.39)	0.43
Poor self rated health		1.98 (1.47-2.67)	<0.001
Difficulty making ends meet		0.96 (0.79-1.17)	0.72
Living alone		1.03 (0.96-1.11)	0.36
More than one fall in the last 6 months		1.27 (1.15-1.39)	<0.001
Taking more than 5 medications		1.49 (1.37-1.61)	<0.001
Carstairs index	1st (highest)	1	(-)
	2nd	1.13 (1.00-1.27)	0.04
	3rd	1.15 (0.99-1.34)	0.07
	4th	1.17 (1.02-1.33)	0.02
	5th (lowest)	1.26 (1.10-1.44)	<0.01
MMSE	<=23**	1.42 (1.27-1.59)	<0.001
High alcohol	Men	1.07 (0.88-1.32)	0.48
	Women	0.78 (0.54-1.13)	0.18

Table 8.8 Hazard ratio for diabetes using all variables

*All variables mutually adjusted **indicates cognitive impairment

The other criteria for inclusion in the final model were the affect each variable had on the adjusted hazard ratio for diabetes. These are shown in table 8.9 after the subsequent inclusion of each additional variable. Age and sex both altered the crude hazard ratio by approximately five percent. Age and sex are both factors that one would have expected to include in an adjusted hazard ratio. The other variables are therefore presented after they have been adjusted for age and sex. The table shows that in each instance none of the variables alters the hazard ratio by more than five percent. Therefore the final parsimonious model contains only age and sex. The final adjusted hazard ratio for death from diabetes was therefore 1.50 (95% CI, 1.38-1.65).

	Hazard Ratio, (95% CI)	P value
Crude HR diabetes	1.48 (1.35-1.61)	(-)
Variable	Adjusted HR diabetes	
Age group	1.55 (1.42-1.96)	<0.001
Sex*	1.50 (1.38-1.65)	<0.001
Smoking^	1.53 (1.39-1.67)	<0.001
BMI^	1.53 (1.38-1.67)	<0.001
WHR (women)*	1.43 (1..24-1.65)	<0.001
More then one fall in the last six months^	1.48 (1.34-1.56)	<0.001
Greater than 5 mdeciations^	1.43 (1.30-1.56)	<0.001
Previous MI^	1.51 (1.36-1.66)	<0.001
Previous CVA^	1.47 (1.34-1.61)	<0.001
Proteinuria^	1.49 (1.35-1.65)	<0.001
Raised Creatinine^	1.46 (1.34-1.60)	<0.001
Poor self rated health^	1.53 (1.39-1.67)	<0.001
Carstairs index^	1.49 (1.36-1.64)	<0.001
MMSE^	1.48 (1.35-1.62)	<0.001

Table 8.9 Hazard ratio for diabetes after adjustment for individual variables
*Adjusted for age, ^Adjusted for age and sex

The Kaplan-Meier survival graph for all cause mortality for people with and without diabetes is given in figure 8.2.

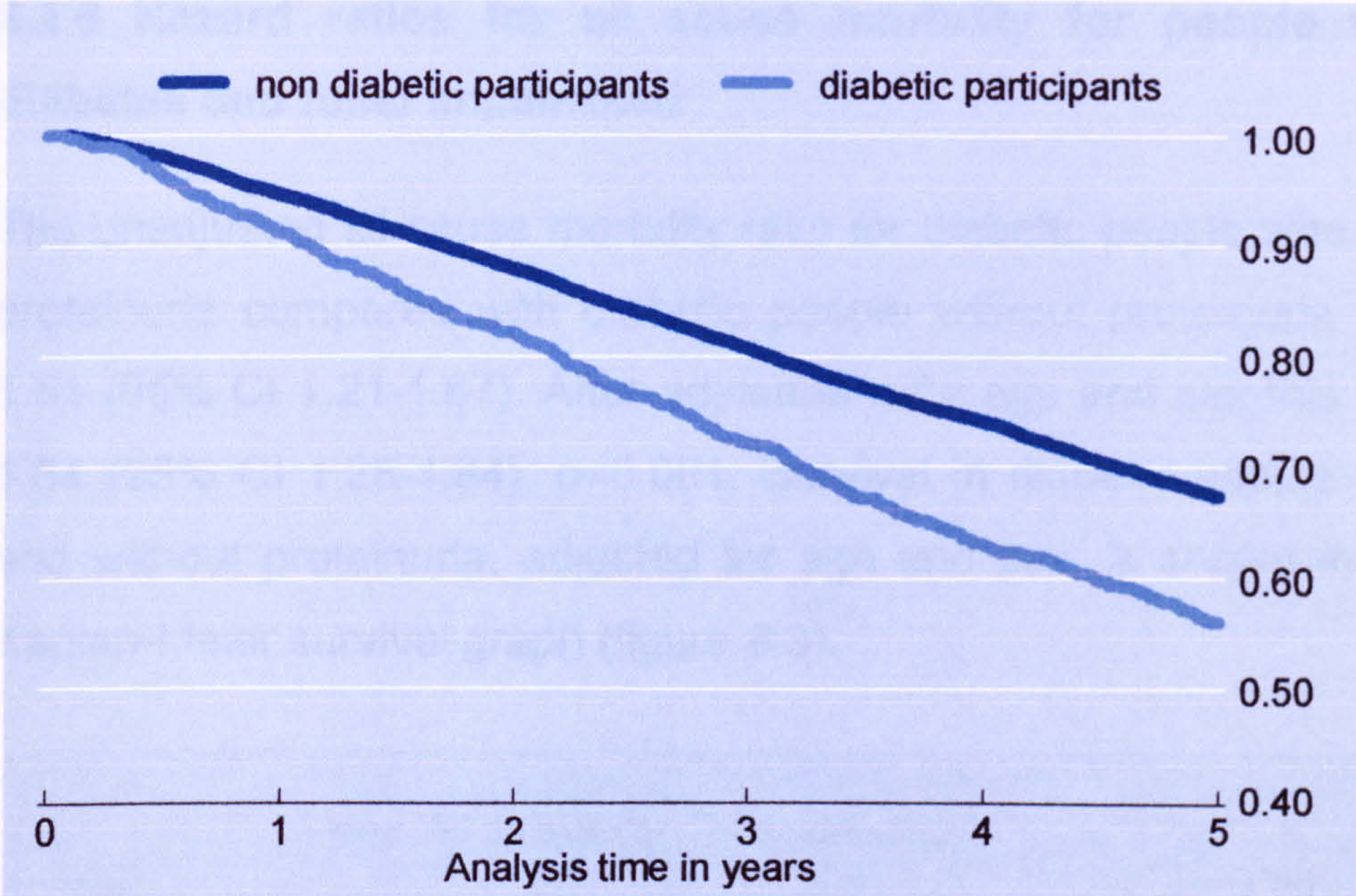


Figure 8.2. Kaplan-Meier survival estimates for all cause mortality

8.4.4 Age and sex specific hazard ratios for all cause mortality in people with diabetes

Hazard ratios were calculated for each age group (75-79 years, 80-84 years, 85-89 years and 90 plus years) for men and women. The results are shown in table 8.10.

		Hazard ratio (95% CI)	P value
Men	75-79 years	1.55 (1.27-1.89)	<0.001
	80-84 years	1.47 (1.16-1.86)	0.002
	85-89 years	1.62 (1.25-2.11)	<0.001
	90 plus	1.19 (0.66-2.15)	0.56
Women	75-79 years	1.70 (1.33-2.17)	<0.001
	80-84 years	1.42 (1.14-1.78)	0.002
	85-89 years	1.52 (1.17-1.97)	0.002
	90 plus	1.27 (0.91-1.78)	0.17

Table 8.10 Age and sex specific hazard ratios for diabetes

8.4.5 Hazard ratios for all cause mortality for people with diabetes and renal impairment

The unadjusted all cause mortality ratio for diabetic people who had proteinuria compared with diabetic people without proteinuria was 1.51 (95% CI 1.21-1.87). After adjustment for age and sex this was 1.54 (95% CI 1.28-1.84), $p<0.001$. Survival in diabetic people with and without proteinuria, adjusted for age and sex, is shown in the Kaplan-Meier survival graph (figure 8.3).

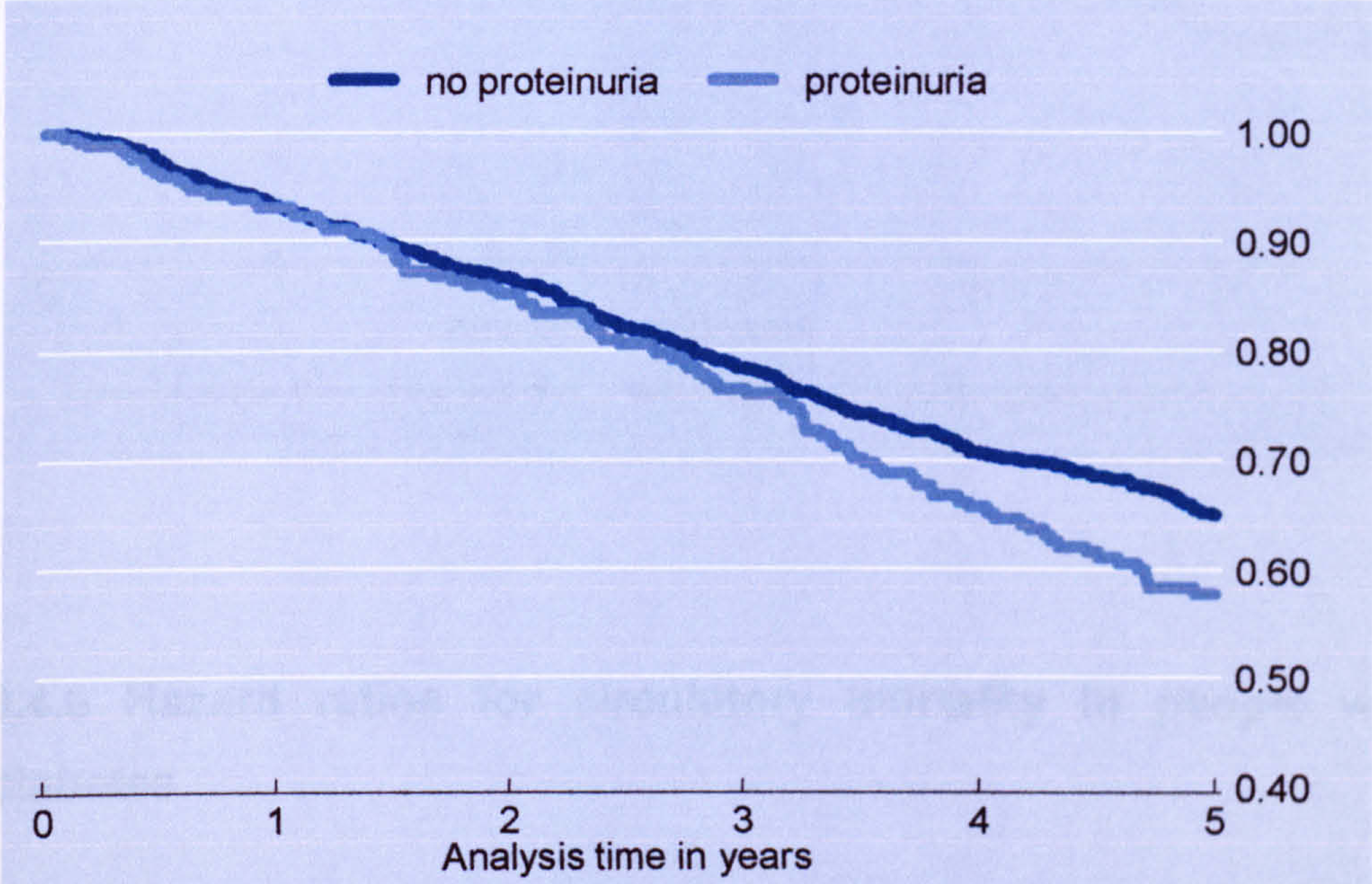


Figure 8.3. Kaplan-Meier survival estimates for diabetic people with and without proteinuria

The unadjusted all cause mortality ratio for diabetic people who had raised creatinine was 1.78 (95% CI 1.42-2.24). After adjustment for age and sex this was 1.53 (95% CI 1.19-1.98), $p=0.001$. The addition of further variables were not significant in the Cox proportional model and hence not included. Survival in diabetic people with and without raised creatinine, adjusted for age and sex, is shown in the Kaplan-Meier survival graph (figure 8.4).

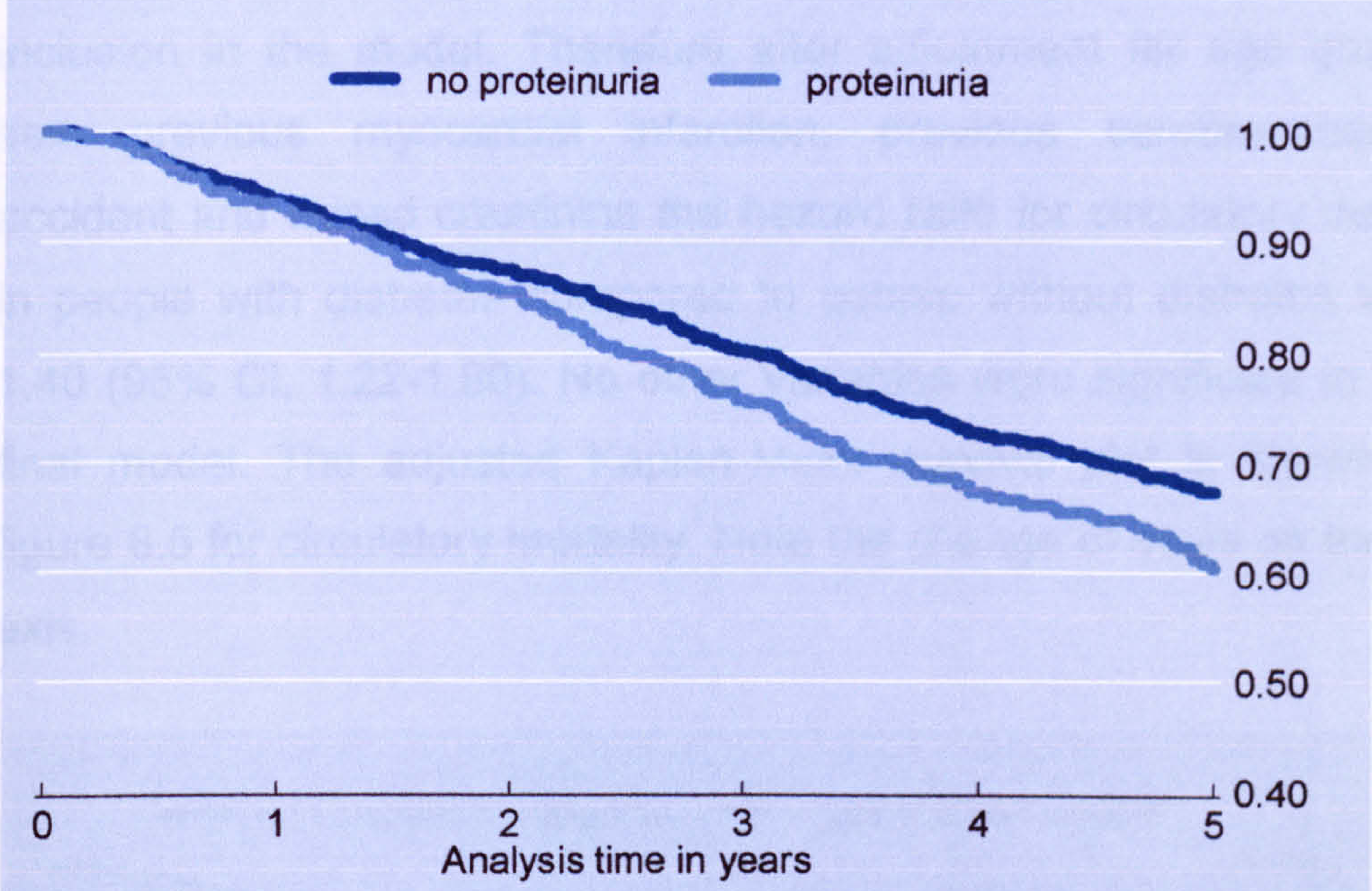


Figure 8.4. Kaplan-Meier survival estimates for diabetic people with and without rasied creatinine

8.4.6 Hazard ratios for circulatory mortality in people with diabetes

The unadjusted hazard ratio for circulatory mortality in people with diabetes compared with non diabetic people was 1.57 (95% CI, 1.39-1.77). When all possible factors were tested in the Cox proportional hazards model raised systolic, raised diastolic, anyone to call for help and alcohol were not significant and were excluded from future use. When the remaining variables were assessed, to ascertain their affect on the hazard ratio, five were found to alter the hazard ratio by over five percent. These were age group, sex, previous myocardial infarction previous cerebrovascular accident and raised creatinine (all, $p<0.001$). The final parsimonious model included all of these factors. None of the other variables altered the hazard ratio for circulatory death to an extent which warranted their inclusion in the model. Therefore after adjustment for age group, sex, previous myocardial infarction, previous cerebrovascular accident and raised creatinine the hazard ratio for circulatory death in people with diabetes compared to people without diabetes was 1.40 (95% CI, 1.22-1.60). No other variables were significant in the final model. The adjusted Kaplan-Meier survival plot is shown in figure 8.5 for circulatory mortality. Note the change of scale on the y-axis.

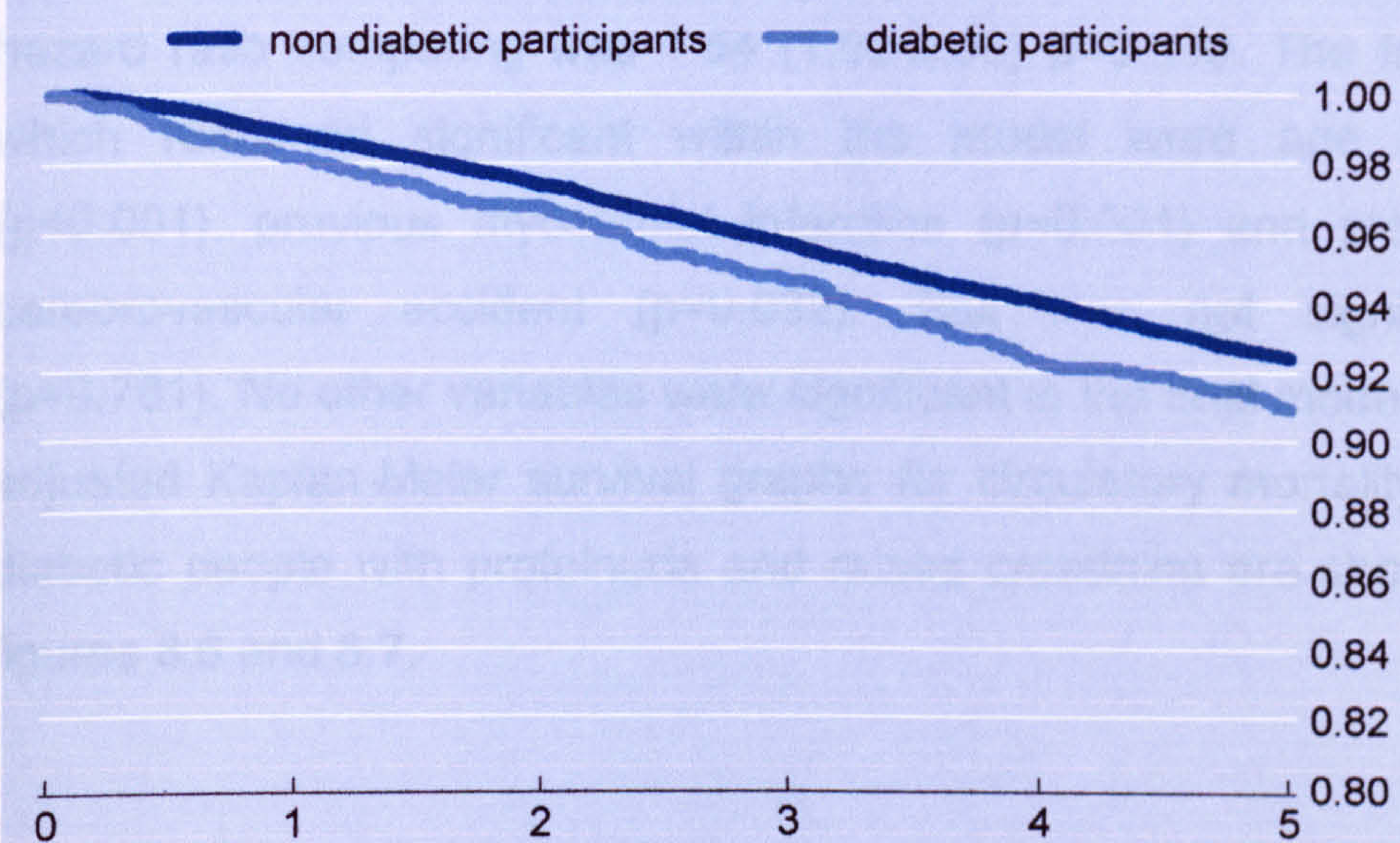


Figure 8.5. Kaplan-Meier survival estimates for circulatory mortality

8.4.7 Hazard ratios for circulatory mortality in people with diabetes and renal impairment

In diabetic participants with proteinuria the unadjusted hazard ratio was 1.46 (95% CI, 1.12-1.91) compared to diabetic people without proteinuria. The adjusted hazard ratio was 1.41 (1.10-1.81). The variables which remained significant in the final model were age group ($p<0.001$) previous myocardial infarction ($p<0.001$) and previous cerebrovascular accident ($p=0.007$). Sex was not significant ($p=0.84$). No other variables were significant in the final model. In diabetic participants with raised creatinine the unadjusted hazard ratio for circulatory death was 1.79 (95% CI, 1.24-2.59) compared to diabetic people without raised creatinine. The adjusted hazard ratio comparing was 1.54 (1.02-2.36) $p=0.039$. The factors which remained significant within the model were age group ($p<0.001$), previous myocardial infarction ($p<0.001$) and previous cerebrovascular accident ($p=0.032$). Sex was not significant ($p=0.781$). No other variables were significant in the final model. The adjusted Kaplan-Meier survival graphs for circulatory mortality and diabetic people with proteinuria and raised creatinine are shown in figures 8.6 and 8.7.

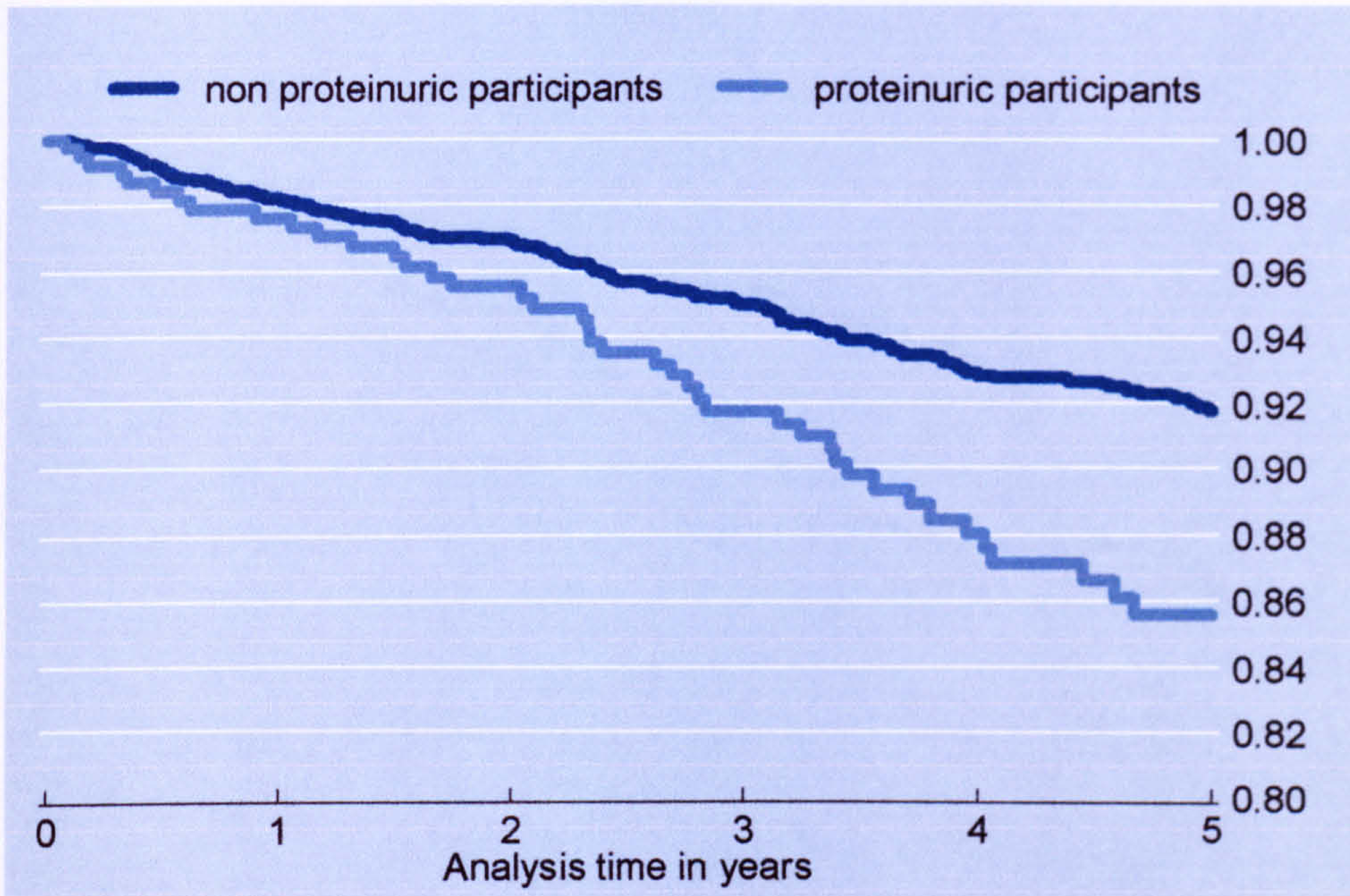


Figure 8.6. Kaplan-Meier survival estimates for circulatory mortality in diabetic participants

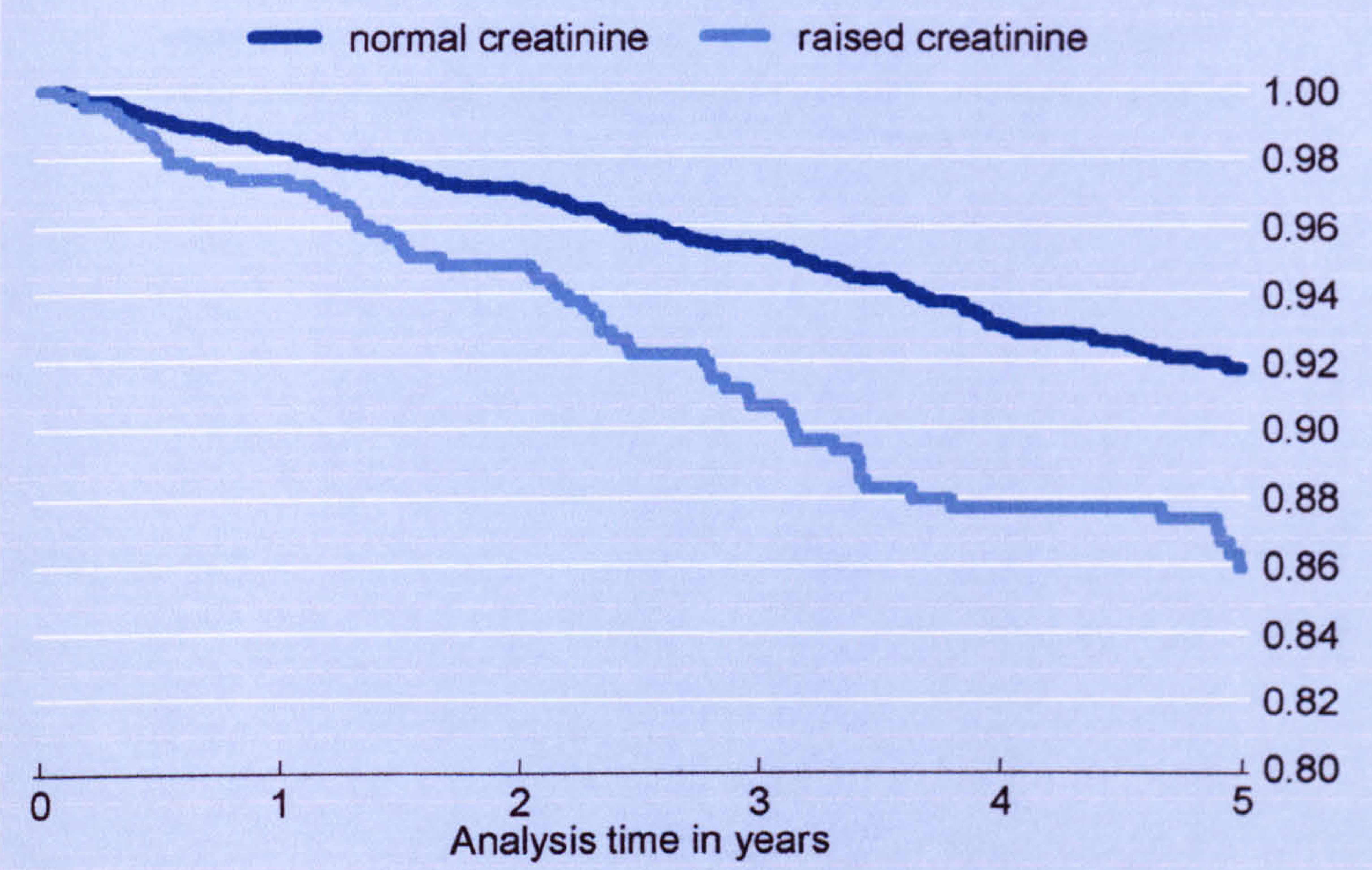


Figure 8.7. Kaplan-Meier survival estimates for circulatory mortality in diabetic participants

8.4.8 Hazard ratios for renal mortality in people with diabetes

The unadjusted hazard ratio for renal mortality in trial participants with diabetes compared to trial participants without diabetes was 2.45 (95% CI, 1.53-3.94). After adjustment the hazard ratio was 1.98 (1.14-3.44) ($p=0.015$) comparing the two groups (people with and without diabetes). Age group ($p<0.001$), raised creatinine ($p<0.001$) and proteinuria ($p=0.003$) were all significant in the final model. Sex was not significant within the model ($p=0.334$). No other variables were significant in the final model. The adjusted Kaplan-Meier survival graph is shown in figure 8.8, note the change of scale on the y-axis.

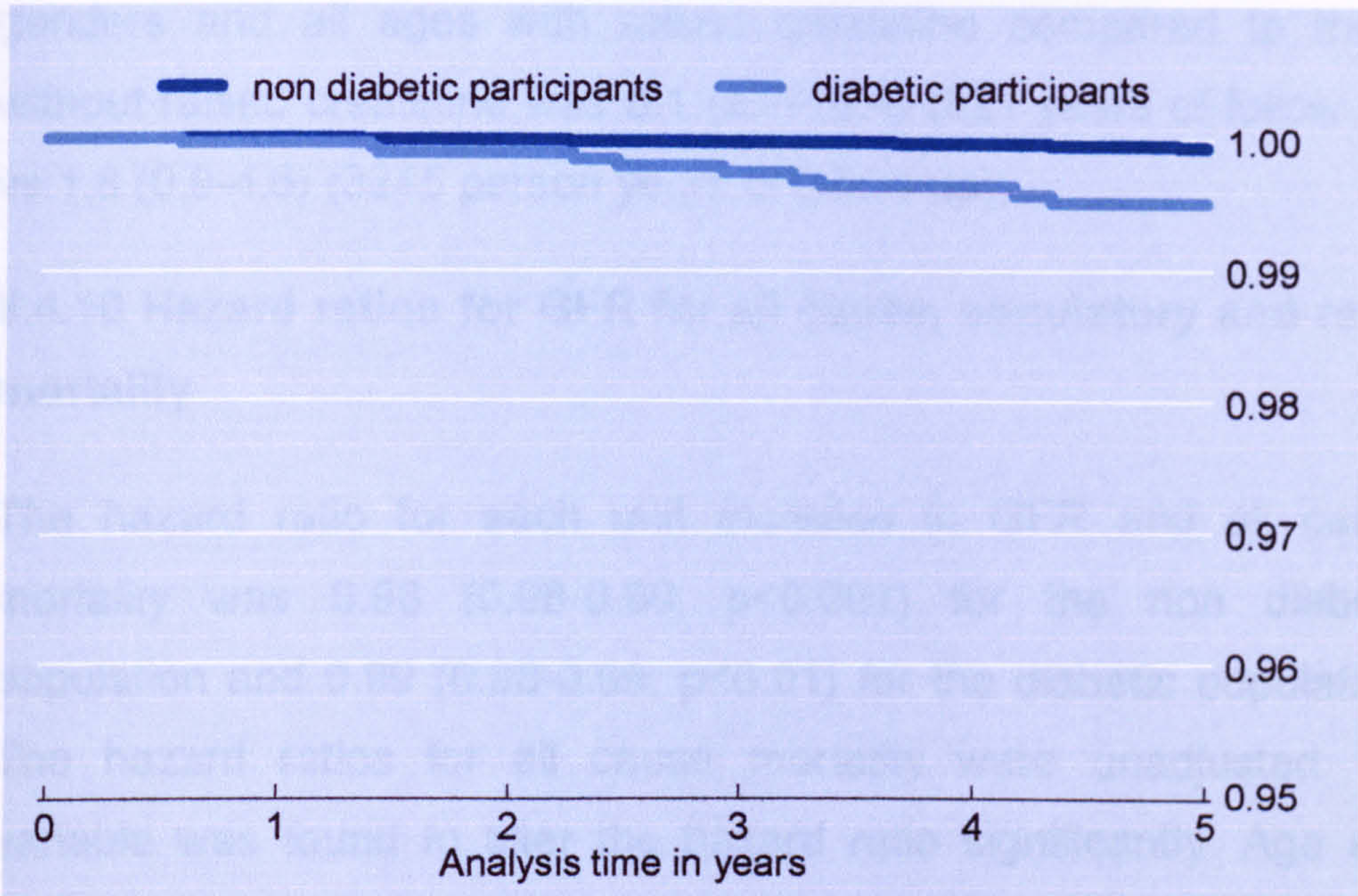


Figure 8.8. Kaplan-Meier survival estimates for renal mortality in diabetic participants

8.4.9 Hazard ratios and rates of death for renal mortality for people with diabetes and renal impairment

The unadjusted hazard ratios for renal mortality in diabetic people with and without proteinuria and raised creatinine were 4.01 (1.41-12.05) and 3.42 (1.12-10.26) respectively. After adjustment for age group and sex they were 2.90 (0.75-11.12) and 3.31 (0.91-12.38) respectively. However, both of these results should be treated with caution as visual inspection of the proportional hazards ratio showed that neither ratio was maintained.

The rate of renal mortality (per 1000 person years) for people with diabetes of both genders and all ages with proteinuria compared to those without proteinuria was 8.9 (4.0-22.6) (676 years of follow up) vs 2.2 (1.1-5.0) (3593 person years of follow up). The rate of renal mortality (per 1000 person years) for people with diabetes of both genders and all ages with raised creatinine compared to those without raised creatinine was 6.1 (2.7-16.4) (821 years of follow up) vs 1.8 (0.9-4.6) (3245 person years of follow up).

8.4.10 Hazard ratios for GFR for all cause, circulatory and renal mortality

The hazard ratio for each unit *increase* in GFR and all cause mortality was 0.98 (0.98-0.99, $p<0.001$) for the non diabetic population and 0.99 (0.98-0.99, $p<0.01$) for the diabetic population. The hazard ratios for all cause mortality were unadjusted. No variable was found to alter the hazard ratio significantly. Age and sex have been used in the calculation of GFR using the MDRD equation and were therefore not included in the Cox proportional model.

The hazard ratio for circulatory disease and each unit *increase* in GFR was 0.98 (0.98-0.98, $p<0.001$) in the non diabetic population and 0.98 (0.97-0.99, $p<0.01$) in the diabetic population. For renal death the hazard ratio for each unit *increase* in GFR was 0.95 (0.92-0.98, $p<0.01$) for the non diabetic population and 0.94 (0.88-0.97, $p=0.04$) for the diabetic population. All the final Cox models remained unadjusted because no variables were found to improve the final models and were therefore not used.

The hazard ratio for GFR below 60 ml/min per 1.73 m^2 and all cause mortality was 1.32 (1.01-1.44, $p<0.001$) for the non diabetic population and 1.21 (0.99-1.48, $p=0.06$) for the diabetic population. The hazard ratios for all cause mortality were unadjusted. The hazard ratio for circulatory disease and GFR below 60 ml/min per 1.73 m^2 was 1.54 (1.36-1.75, $p<0.001$) in the non diabetic population and 1.45 (1.08-1.96, p=0.01) in the diabetic population. For renal death the hazard ratio for GFR below 60 ml/min per 1.73 m^2 was 1.86 (1.08-.322, p=0.03) for the non diabetic population and 2.25 (0.67-7.61, p=0.19) for the diabetic population. The hazard ratios were again unadjusted.

8.5 Discussion

8.5.1 Introduction

The results presented in this thesis represent the most comprehensive estimate of mortality rates and cause of death in the older diabetic person undertaken in the UK. The results for the very oldest age groups (over 90 years) appear to be the first estimates of the risk and rate of death to be described.

8.5.2 Non responding participants

The increased numbers of deaths and the raised hazard ratios for death of the non responding participants compared to the responding participants were consistent with the results one would have expected. Each result showed that non responders were more likely to die than responders. Non responders had a higher proportion of deaths, 47.0% vs 33.6%, a higher rate of death (per 1000 person years), 119.4 (109.7-130.3) vs 80.3 (76.3-84.5) and an increased hazard ratio for death 1.49 (1.38-1.62) vs 1.0.

It is extremely difficult to ensure complete participation of eligible people in any cohort study. People who do agree to participate are likely to be different from those who do not participate(299). Participants may vary in several ways. They may have different levels of attitudes towards health, personal motivation, risk factor status and be in poorer health(300). The MRC trial did not contain information regarding exposure status for any of the non responders (other than age and sex). It contained data relating to death; outcome data. Therefore, in the MRC study, non response could only be related to outcome. In epidemiological studies when only outcome data is available for every participant involved in the study, regardless of responder status, the death rates generated for the responding participants will be an underestimate. This is due to the overall poorer health of those who did not respond. However, beyond simply reporting the increased death rates for all ages and genders and highlighting the possible reasons for this, no further information regarding these people existed in the MRC trial. Further information was unavailable as it was deemed unethical to obtain additional information in people without their consent. Therefore non responders could not be described further.

8.5.3 Hazard ratios and rates of death for diabetes and all cause mortality

8.5.3.1 The Hazard ratio and the statistical model used

In the final model, the hazard ratio for death in people aged over 75 years with diabetes compared to those without diabetes was 1.50 (1.38-1.65), $p<0.001$. The figure was only adjusted for age and sex. The hazard ratio for the saturated model, which included all potential variables in the Cox proportional hazard model, was 1.42 (1.27-1.59). The reasons that I chose one model over the other and only adjusted for age group and sex warrant discussion. Firstly, the predetermined modelling strategy stated that factors would only be included in the final model if they were significant within that model and altered the hazard ratio by at least five percent; only age and sex met these criteria. While the hazard ratio for the saturated model differed from the overall hazard ratio by five percent no single variable other than age and sex altered it significantly and hence were not included. Secondly, variables were decided a priori. Therefore every variable, used during the course the thesis, was tested in the Cox proportional hazard model. Finally the use of the most parsimonious model as possible has many advantages; primarily simplicity and reproducibility. My final model was extremely parsimonious.

8.5.3.2 The hazard ratio and death rates for different age groups and gender

The results of the MRC trial showed that diabetes continued to be a contributory factor for death until the extremes of old age, in both men and women. The adjusted hazard ratios for death in people with diabetes were consistently elevated until above the age of 90 years. Prior to 90 years of age the hazard ratios did not show any increasing or decreasing trends and were all approximately 1.50. Gender did not produce different results. For both men and women the hazard ratios for death were above one and did not differ to any large extent between the sexes. Above the age of 90 years the hazard ratio remained above one but the 95% confidence interval encompassed one for both men and women. However, the absolute rate of death was higher for men and the low number of deaths (14) and wide confidence intervals for men with diabetes aged over 90 years should be highlighted. It was therefore likely that a lack of statistical power was responsible for failure to clearly demonstrate a difference in the rate of death or hazard ratio for the oldest groups of men and women with diabetes.

8.5.3.3 How did the results from the MRC trial compare with other trial results?

The problems drawing comparisons with other studies

The MRC trial generated hazard ratios and rates of death for four age groups above 75 years and for both sexes. Therefore the results could not be compared exactly to all the studies which were discussed in the introduction to this chapter, as many of them did not provide results for the same groupings. For example, the most comparable study to the MRC study was the large self reported questionnaire conducted in Canada(161). The results produced from the Canadian study were only presented for a combined group of men and women aged over 65 years, without providing subgroup analysis. In addition, the trial results discussed in the introduction provided a variety of “estimates” of death; relative rate of death, death rates, hazard ratios, relative risks or Standardised Mortality Ratios and therefore direct statistical comparison was difficult. In spite of these limitations, I have made attempts to compare my results with those from previous trials. I have done so my comparing my results in terms of age group and by gender as closely as possible to previous studies.

Age group

My results for the hazard ratios of death from all cause mortality were different to the other studies reported. The hazard ratios generated from the MRC trial for people aged 80-84 years and 85-89 years were higher than previous estimates. Previous trials showed that the effect estimates for death comparing people with and people without diabetes, while remaining elevated, tended to become nearer one with increasing age(57;58;60;279;285). Each study showed that the affect of diabetes tended to decrease, while remaining elevated, with each increase in age group. None of these studies specifically reported hazard ratios for people aged over 90 years. The five most comparable studies included the Melton study lead by Croxson(279), the Italian study by Bruno *et al*(58), the US Medicare study(57), the Verona diabetes study(285) and the South Tees study(60). The Melton study showed that the hazard ratio for death from diabetes decreased from 6.96 (2.99-16.21) for ages 75-79 years, to 2.48 (0.78-7.86) for ages 80-84 years and 1.34 (0.37-4.93) for people aged over 85 years. The author noted that the confidence intervals were wide due to sample size and low numbers of deaths(301). The Italian study calculated SMRs for a combined group of men and women with diabetes. The SMRs declined from 1.86 (1.52-2.25) for people aged 60-69 years to 1.12 (0.98-1.27) for people aged over 80. The Medicare study showed that the relative risk of death from diabetes declined from 2.11 (2.05-2.17) for people aged 75-79 years, 1.85 (1.80-1.90) for those aged 80-84 years and 1.46 (1.43-1.49) for those aged over 85 years. In the Verona diabetes study SMRs declined markedly with increasing age group. In the oldest age group (75 plus years) the SMR was 1.13 (1.00-1.28) for men and 1.32 (1.20-1.44) for women. While the South Tees study did not use exactly the same age groupings as other studies, the results again showed decreasing relative risks of death with increasing age group. For people aged 60-79 years the relative risk of death was 1.96 (1.74-2.21) for men and 1.41 (1.28-1.56) for women. In the oldest age group (80 plus years) the relative risks were 1.25 (1.09-1.43) for men and 1.09 (0.92-1.29) for women.

There were two previous studies which published actual rates of death(60;288). The first study was conducted by McBean which calculated death rates in people with diabetes, for the single year 2001, using the Medicare system (288). Their results showed a death rate (per 1000 persons per year) of 75.1 for people aged 75-79 years, 112.5 for ages 80.84 years and 202.2 for ages over 85 years. The results obtained from the MRC trial were similar; for the same age groups the results were 81.8, 116.0 and 201.9, respectively. The rate for those aged over 90 was 268.2, in the MRC trial. Both studies were undertaken at approximately the same time, among predominantly white populations. Comparison of the two studies showed that the rates of death for people with diabetes in the UK were not different to those in North America, although direct comparison of rates between the studies may have been inappropriate. The Medicare study was based on claims data, the sensitivity of which has been estimated to be 63.4%. This is a lot lower than that obtained for the MRC trial, estimated as 88.5% (see section 3.6.8). Consequently the American study may have represented the true rates in North America for Medicare claimants, while the MRC trial was a more accurate representation of the true rate of death for people living in the community with diabetes in the U.K. The Medicare study was undertaken to assess changes in death rate and incidence since 1994, with 2001 being the last year recorded. Therefore it did not include comparisons with non diabetic groups and it was not possible to assess whether the affect of diabetes on mortality declined with increasing age from this study. The second study which published rates was the South Tees group. They South Tees group published the rates of death from which the relative rates of death were calculated for men and women(60). The rate of death for the men aged over 80 years was 155.56 (95% CI, 143.67-167.45) and 134.55 (127.70-141.41) for women. The results from the MRC trial were 144.0 (114.8-182.0), 244.4 (186.8-321.8) and 327.5 (200.0-538.4) for men aged 80-84 years, 85-89 years and 90 plus years respectively The rates of death for same age groups of women were 98.1 (78.8-122.7), 117.2 (140.3-223.7) and 248.5 (187.4-332.1). Both sets of results would appear to be similar, with the South Tees results reflecting an average figure of the MRC trial results if all the different age groups had been combined.

Gender

The hazard ratios for mortality comparing people with and people without diabetes for both men and women were both raised until past the age of 90 years. They were all approximately 1.50 and did not differ between the sexes. This contrasted with many of the previous studies which have shown inconsistent affects of sex(285-287;301;302). In the Melton study, after 4.5 years of follow up men aged over 75 years had a survival of under 40% compared to over 50% for women. The large Medicare study showed that compared to men with diabetes aged over 65 years women had a higher relative risk of death; 1.34 (1.31-1.38). The Danish study showed that relative risks of death were higher for women of 75-79 years and 80-84 years; 1.24 vs 0.98 and 1.19 vs 1.02 for the two groups. The Verona diabetes study found SMRs for men aged over 75 years to be 1.13 (1.00-1.28) which were lower than women 1.32 (1.20-1.44). The South Tees data which was described above, showed that in addition to decreasing hazard ratios as diabetic people got older, men had consistently higher hazard ratios than women.

8.5.3.4 Why did the MRC trial produce different results than previous studies?

Due to the size of MRC trial and the large numbers of elderly diabetic people involved it was likely that the results generated for age reflect the true affect of diabetes in the older person. Previous estimates were derived from studies that may not have been big enough to detect true differences. And this lack of statistical strength, seen in the other studies, should be highlighted as a limitation in the MRC trial in the very oldest age groups.

Do the similar hazard ratios for all cause mortality generated for men and women represent true results? Why should men and women suffer different biological outcomes from a disease which affects men and women equally. Some of the previous studies which found a higher affect of diabetes in women attributed the results to a survivor affect(285-287). The men were more likely to die from diabetes before they reached older age than women. Once men had become elders the affect the diabetes decreased and tended to contribute to death equally for men and women. Were some of the previous differences between sexes attributable to the age of diagnosis of diabetes? The paper by Tan *et al*(290) suggested that women but not men diagnosed with diabetes at older age had an increased chance of death. The MRC trial did not provide the age of diagnosis of diabetes and hence this theory could not be tested using the MRC trial and must remain a possibility.

8.5.3.5 Other potential biases of the MRC trial

The number of deaths increased massively in all people aged over 90 years, with more than 20% of people aged over 90 years dying each year. The yearly rate of death for people aged over 90 years without diabetes was 214.5 per 1000 people and 268.2 per 1000 people with diabetes. However, in absolute terms only 6% more people aged over 90 years with diabetes died than people aged over 90 years without diabetes over the five year follow up period. It was possible, that due to the extremely high mortality rate from all causes at this age, diabetes had little or no affect.

Could the decreased affect of diabetes in those aged over 90 years have been due to the survivor effect? In a cohort of people with diabetes surviving to older age, diabetes may have already killed susceptible people. This explanation did though seem unlikely. Why should simply living to over 90, rather than ones mid to late eighties, lead to a survivor effect. Could this be a true effect? Is diabetes is a less dangerous condition at the extremes of old age? It again seems implausible that a biological disease should suddenly have less effect at this age, although diabetic older people may not live long enough to develop the complications of diabetes, especially if they were diagnosed with diabetes at an older age.

While it is possible that any results are biased by a multitude of factors, why would the MRC trial results be different to those previously generated from other studies? As discussed elsewhere in this thesis (specifically chapter 9) the number of people detected with diabetes in the MRC trial was likely to have been an underestimate with consequential dilution of any affects seen. Similarly many of the previous studies will have also underestimated the true local diabetic population, either through the use of clinic based populations(280;286) or through the use of claims data(287). Therefore insufficient case ascertainment is an unlikely explanation for the differences seen between the MRC trial and previous studies.

Insufficient case ascertainment is also a potential (if unlikely) bias for all the subsequent results discussed in this chapter i.e. circulatory and renal death and the affect of altered renal function on death. However, the bias has been noted here and to avoid repetition it was not discussed further in this chapter.

It is also unlikely that (all cause) death was incorrectly registered. Over 99% of trial participants were registered for mortality and death was not distinguished on the basis of diabetes status. Therefore the results for the all cause mortality should not differ by death registration between the trial participants with diabetes and trial participants without diabetes. In fact, the extremely high rate of death registration, by the ONS, was a strength of the MRC trial.

8.5.4 Hazard ratios and rates of death for diabetes and circulatory mortality

The adjusted hazard ratio for death from circulatory disease in people with diabetes was 1.40 (1.22-1.60). The final Cox model used to generate this figure included previous myocardial infarction, previous cerebrovascular accident and raised creatinine, in addition to age group and sex. A history of previous vascular disease (cardiac or cerebral) represents existing disease and it was not surprising that they significantly altered the outcome. An extensive history of cardiac disease could also have increased the chances of cardiac death being recorded on the death certificate. Another potential confounding effect. Raised creatinine has also been established as a predictor of circulatory disease in diabetic populations(65;295) and its effect in the Cox model supported that.

The results for rates of death from circulatory death were raised in the diabetic groups of all ages and sex compared to the non diabetic group. It was worth noting the results for the male participants with and without diabetes. While the overall rates were different between the two groups 60.7 (50.6-73.6) vs 47.9 (43.9-52.3) the results for individual age groups were very similar for all groups aged over 80 years. The largest difference occurred between the 75-79 year age groups. This lent support to the hypothesis of a survivor effect amongst male diabetic people, at least for circulatory disease. i.e. diabetic males only succumb to circulatory disease at a higher rate than non diabetic males before the age of 80.

The WHO MSVDD showed in a younger diabetic population that cardiovascular mortality accounted for 52% of deaths(292). The results from the older diabetic population in the MRC trial were remarkably similar (51%). This results suggested that there was no change in the overall affect of diabetes on circulatory death between the younger population in the WHO MSVDD and the older diabetic population used in the MRC trial. Direct comparisons with the Verona diabetes study were difficult because that published report provided few specific results for the older person(59). It concluded that diabetes contributed to cardiovascular disease but to a decreasing extent in people aged over 75 years compared to younger age groups. The MRC trial could not make exactly the same comparisons. However, the raised hazard ratio for death from circulatory causes in the older diabetic person implied that diabetes did contribute to circulatory death. The South Tees data also produced outcome measures for cardiovascular death in the older diabetic person. In males aged 60-79, the cardiovascular death rates (per 1000 person years) were 34.46 (31.47-37.46), and 80.50 (74.47-86.53) for men aged over 80 years. For the women aged 60-79 years the rates of death were 34.25 (30.80-37.71) and for women aged over 80 years 72.83 (67.62-78.04). The use of different age structures made direct comparisons difficult but in a similar manner to all cause mortality their results would seem to be a composite of the results obtained from the MRC trial. The paper from the DARTS database which concentrated on the affect of the age of diagnosis of diabetes did not show any increase in cardiovascular disease(290). Age of diagnosis was not determined from the MRC trial and therefore direct comparisons were not possible.

It should also be noted that circulatory disease was identified as the underlying cause of death from the death certificate. This grouping included all forms of cardiac and vascular disease. The vast majority would have been due to cardiac ischaemia or stroke but not all. For example, heart failure is another mode of death which frequently, but not exclusively, results from ischaemic heart disease. What implications does that have when interpreting the results generated? Firstly, it makes direct comparisons with other trials less reliable if those trials assessed specifically cardiovascular death, although it is likely that circulatory death and cardiovascular death represent very similar measures. Secondly, could the use of circulatory death biased the results when compared to cardiovascular death. This would seem a small but real possibility. If people with diabetes suffered from a disproportionately high or low amount of one particular form of circulatory death compared to the non diabetic people the results could have been biased. For example, did diabetic people have a much larger incidence of stroke death (coded as a circulatory death) compared to the non diabetic population? Unfortunately is was not possible to determine this from the data which was available. Finally, from a scientific perspective, it was a pity not to be able to differentiate between exact cardiac disease and cerebrovascular disease more accurately. The potential inaccuracy of the recording of cardiovascular death in this study must be considered as a limitation.

The reporting of cause of death was a potential source of bias in diabetic people with circulatory (and renal) death. Unlike all cause mortality, it was possible that circulatory and renal mortality were recorded differently between trial participants with and without diabetes. It is established that diabetes contributes to vascular and renal disease. Therefore the possibility of recording the cause of death and contributory causes of death differently between people with and people without diabetes must exist. This statement can also be supported from studies of death certificates which showed, that in addition to extremely low levels of reporting diabetes itself, reporting of circulatory disease was higher on death certificates of people with diabetes(298). While the similar results have not been published for renal death, different levels of reporting of renal disease on the death certificates of diabetic and non diabetic people must also exist as a potential bias.

8.5.5 Hazard ratios and rates of death for diabetes and renal mortality

In a younger diabetic population, the WHO MSVDD demonstrated renal disease in 8% of male deaths and 14% of female deaths(292). The MRC trial showed death rates for the whole diabetic cohort to be 2.9%. The percentage of deaths in male diabetic participants was 2.1% and 3.8% in female diabetic participants. While the MRC trial showed a higher percentage in women, overall the percentage of deaths was far lower than the WHO MSVDD. These results may have reflected the true figure of death attributable to renal disease in an elderly population.

However, the extremely lower numbers of overall cases recorded (17) and the large discrepancy between the previous figures and those generated by the MRC trial suggest that the figures from the MRC trial under represented the true figure. The most obvious reason for the low number of renal deaths recorded was that renal disease was not accurately recorded on the death certificate.

However the rates of death from renal disease in the older diabetic person represent the largest estimate currently available. The results showed that for men and women combined renal mortality increased with age group. The other groupings were not really large enough for meaningful conclusions to be drawn from them. In addition, the adjusted hazard ratio for renal mortality in people with and without diabetes was raised 1.98 (1.14-3.44). This result clearly demonstrated that diabetes affects renal mortality in the older diabetic person.

8.5.6 Hazard ratios and rates of death for people with diabetes and proteinuria, raised creatinine and Glomerular Filtration Rate

8.5.6.1 Proteinuria and all cause mortality

The adjusted hazard ratio for all cause mortality was raised for diabetic people with proteinuria compared to those without; 1.54 (1.28-1.84), $p<0.001$. The rates of death were also consistently higher in diabetic people of all age groups and gender. Interestingly the rates of death for men and women were similar for all people aged over 75 years and for individual age groups. Neither was sex significant in the adjusted hazard model. These results implied that among people with diabetes and proteinuria sex did not add predictive information about the likelihood of death. There were 105 deaths and 676 years of follow up which allowed meaningful results to be generated and thus decreasing the likelihood that chance was responsible for this result.

The Manchester study by Jude *et al*(65) showed that increasing proteinuria was associated with all cause mortality in younger diabetic groups. Similar results in the older diabetic person were supported by our findings. The large Italian study by Bo and colleagues(295) assessed several aspects of renal function and death in diabetic people of all ages. The study included some people aged over 75 years and showed that the hazard ratio for death in people with microalbuminuria was 2.08 (1.69-2.56). In this study microalbuminuria was defined as an albumin excretion rate of 20-199μg/min. The MRC study detected the presence of protein in the urine without quantifying the exact amount which made direct comparisons difficult. Regardless, the MRC study only included older people and confirmed that proteinuria continues to predict all cause mortality into older age.

8.5.6.2 Proteinuria and circulatory mortality

The adjusted hazard ratio for death from circulatory disease in diabetic people with and without proteinuria was 1.41 (1.10-1.81), $p<0.001$. The rates of death were also raised in diabetic people with proteinuria. However, unlike all cause mortality, women tended to have higher rates of death. Unfortunately the small number of circulatory deaths in the diabetic proteinuric group made the results of the death rates unreliable.

The raised hazard ratio did imply that proteinuria predicts circulatory death in the older diabetic person, an idea first confirmed on a worldwide basis, in younger diabetic people by Fuller *et al* in the WHO MSVDD(303). The Italian study discussed above(295) did not assess circulatory death per se but did show that the hazard ratio for coronary artery disease was raised (5.45 (3.27-9.08)) in diabetic people with microalbuminuria of a mixed age range.

8.5.6.3 Raised creatinine and all cause mortality

Diabetic people with raised creatinine had an adjusted all cause hazard ratio for death compared to diabetic people without raised creatinine of 1.53 (1.19-1.98), $p<0.001$. The rates of death were consistently higher in diabetic people with raised creatinine compared to those with normal creatinine. Within the diabetic group with raised creatinine the rates of death increased with increasing age group and were very similar between the sexes.

Once again, the Italian study provided a good comparison group. In their trial participants with raised creatinine (defined as above 114.5 µmol/l for men and above 106.1 µmol/l for women, compared to above 120 µmol/l for men and women in the MRC trial) had a hazard ratio for all cause mortality of 3.48 (2.67-4.46). Another good comparison can be drawn from the South Tees study(60). In the 30 participants aged over 80 years with creatinine greater than 150 µmol/l they demonstrated a death rate of 260.90 (202.35-319.46). This would once again appear to be a composite of the combined aged groups aged above 80 years in the MRC trial.

8.5.6.4 Raised creatinine and circulatory mortality

The next group of results which needed consideration were between diabetic people with and without raised creatinine and circulatory mortality. The adjusted hazard ratio was 1.54 (1.02-2.36), $p=0.039$. The rates of death were higher for diabetic people with raised creatinine compared to those without raised creatinine. In the group with raised creatinine the rates increased with age group. Women also appeared to have a higher death rate. It was likely that the potential sex difference may have been spurious. The male age group of 80-84 years appeared to be a very low rate hence resulting in overall bias.

The Manchester group(65) assessed cardiovascular mortality and found it to be raised in younger diabetic people with renal impairment. They used a composite measure of "nephropathy" to do this. This grouping included both albuminuria and raised creatinine. Thus the comparisons between this study and the MRC trial were limited. Again the Italian study provided one of the best comparisons available(295). They showed that the hazard ratio for coronary artery disease in their diabetic participants with raised creatinine was 5.87 (3.08-11.2) compared to diabetic participants without raised creatinine.

8.5.6.5 Renal mortality, proteinuria and raised creatinine

Renal mortality and proteinuria in people with diabetes was increased. Comparing renal mortality in diabetic people with proteinuria to those diabetic people without proteinuria the mortality rate (per 1000 person years) was 8.9 (4.0-22.6) vs 2.2 (1.1-5.0). Renal mortality in diabetic people with and without raised creatinine was also raised. The rate of death (per 1000 person years) was 6.1 (2.7-16.4) vs 1.8 (0.9-4.6). While lack of statistical power hampered both sets of results, unsurprisingly, it seemed likely that renal impairment contributed to a renal cause of death.

8.5.6.6 Glomerular Filtration Rate, all cause, circulatory and renal mortality

Worsening renal function, measured using the modified MDRD equation was shown to be a good predictor of death in both the diabetic and the non diabetic populations. This was true for all cause mortality, circulatory mortality and renal mortality. The associations were strongest in the non diabetic population but persisted in the diabetic population. These results form the first estimation of the ability of the GFR calculated using the MDRD equation to predict death in an exclusively older population. The results generated in this thesis support those of Go and colleagues(296) who showed that worsening GFR was associated with an increased risk of death and cardiovascular death in a large population with a mean age of 52.2 years. When GFR above and below 60 ml/min per 1.73 m^2 was assessed poor renal function was reflected in an increased hazard ratio for all cause, circulatory and renal death. In the diabetic population all the hazard ratios were above one but the only significant result was for circulatory death (1.45, 95%Ci 1.08-1.96, p=0.01). These results imply that especially in non diabetic populations GFR below 60 ml/min per 1.73 m^2 is associated with death.

8.6. Conclusions

The hazard ratios obtained from this thesis represent a large and accurate estimate of the affect of diabetes on mortality in the older person. The results are different to previous estimates and suggested that diabetes increased mortality risk until at least the age of 90. It was also likely that the absence of significant results seen in diabetic people aged over 90 years was due to a lack of statistical power. In contrast to pervious studies the detrimental affect did not show evidence of declining but remained consistently raised. The results for gender showed that mortality rates for men and women were equally affected by the disease.

Diabetes affected all cause, circulatory and renal mortality. These findings were similar to results obtained from younger populations and those obtained from the South Tees study. As well as confirming the South Tees findings the results provided a more accurate picture of diabetes in a broader range of older age groups and gender in the U.K.

Proteinuria, raised creatinine and decreasing GFR were also shown to be independent risk factors for all cause and circulatory mortality.

The MRC trial results confirmed that diabetes remains an important cause of mortality in older people. Diabetes did not become more benign and therefore should be considered as an important health problem, on both an individual level and a population level in the older person. It requires health planning and adequate provision for the needs of the older diabetic person.

Now the importance of diabetes has been established as an important issue the next logical step would be to establish randomised controlled trials to establish appropriate and beneficial care of the older person with diabetes.

Chapter 9. Discussion

9.1 Introduction

This chapter provides an overall summary of the results of this thesis, a general discussion of the thesis and future recommendations.

General discussion of methodological and epidemiological points, relevant to the whole thesis are given in this section in order to avoid repetition within each of the previous chapters. For example, how did the original trial design or the selection of diabetic participants, affect the results generated? As discussion of some points relevant to specific chapters has already been provided, not all of this material is discussed again here in detail.

9.2 Summary of results

9.2.1 The prevalence of diabetes

Due to the age of the participants in the MRC trial, only participants with type 2 diabetes were identified. The methods used to identify diabetic people were a combination of self reporting, identification of high random glucose, identification of diabetic medication and searching of selected GP records. In total, 1177 diabetic people were found. The total population in the MRC trial was 15095. The overall prevalence of diabetes was therefore calculated to be 7.80% (7.11-8.47). Included in this figure are 130 people who were classified as having diabetes based solely on a high random glucose. These people constitute the estimation of undiagnosed diabetes, which was found to be 0.86% (0.96-1.02).

The age specific prevalence rates were 8.31% (7.56-8.49) for people aged 75-79 years, 7.65% (6.89-8.49) for 80-84 years, 6.84% (5.60-8.33) for 85-89 years and 7.14% (5.61-9.05) for people aged 90 plus years. These results are similar to previous prevalence estimates; namely that the prevalence of diabetes increases with age and then tends to plateau at the extremes of old age. The prevalence of diabetes was higher in men, 9.42% (8.44-10.50) than in women, 6.79% (6.10-7.56). The prevalence estimates generated by the MRC trial represent the largest community based survey conducted in diabetic people of this age.

By comparing the questionnaire responses with the available GP records, sensitivity and specificity estimates for self reported clinically diagnosed diabetes were calculated to be 88.5% and 99.9% respectively. These results imply that over 10% of people had a diagnosis of diabetes but did not know it, while very few people wrongly reported having diabetes.

9.2.2 The prevalence of the complications of diabetes

Diabetic people had a higher prevalence of both visual impairment and blindness (Snellen acuity <3/60) compared to the non diabetic population. The prevalence of visual impairment, defined as vision less than Snellen acuity <6/18 in the best eye, in the diabetic population was 13.26%. In the non diabetic population the prevalence of visual impairment was 9.80%. The population attributable risk fractions (PAF) attributable to diabetes assuming complete causality, and low vision and blindness, were 3.46% and 1.02% respectively. Direct comparisons to previous studies were limited because previous studies had focused on diabetic retinopathy, rather than visual impairment. However, these results clearly show that diabetes contributes to the causes of eye disease.

The diabetic population demonstrated an increased prevalence of proteinuria and raised creatinine compared to the non diabetic population. The prevalence rates were 15.97% and 22.65% respectively. In the non diabetic population the prevalence rates were 10.15% and 13.27% respectively. The PAF for proteinuria attributable to diabetes was 6.99% and for raised creatinine 5.35%. The results from the MRC trial represent by far the largest community based estimates published. Surprisingly, raised creatinine levels were not reflected in decreased GFR measurements, calculated using the MDRD equation. This point is expanded later in this chapter.

Angina was more common in people with diabetes compared to people without diabetes. The prevalence was found to be 12.10% and the PAF for angina attributable to diabetes was 3.31% The prevalence was 10.41% in the non diabetic group. A history of myocardial infarction was present in 16.14% of the diabetic population, which was higher than the non diabetic population (10.62%). The PAF attributable to diabetes for myocardial infarction was 4.82%. Cerebrovascular accidents were also more likely to occur in people with diabetes compared to people without diabetes. The prevalence of cerebrovascular accidents was 13.94% in the diabetic population compared to 8.93% in the non diabetic population. The PAF attributable to diabetes in people who have suffered from a cerebrovascular accident was 2.56%. Foot ulcerations were also more likely to occur in diabetic people. The prevalence of foot ulceration was 4.14% compared to 2.80% in the non diabetic population. The PAF attributable to diabetes was 1.09%.

9.2.3 The management and understanding of diabetes in the older person

Over 96% of the people who were aware of their diabetes, were under the care of at least one medical professional. Similarly, over 97% of the population reported managing their condition using at least one form of recognised treatment; diet, medication, insulin or a combination of these. These are extremely high and encouraging figures.

The MRC trial assessed the use of home glucose testing, either urine or blood monitoring. Over 75% of the diabetic population did some form of testing. In the 75% of people who did test, 58% tested at least once per week. Roughly two thirds (63.5%) of older diabetic people were taking medication which was capable of inducing hypoglycaemia. Nearly one quarter of them (23.4%) reported experiencing a hypoglycaemic attack. Nearly half (48.7%) gave an incorrect response when asked about the correct management of their condition in time of illness and over 30% gave incorrect responses to questions about hypoglycaemia and "sick day" management.

There appeared to be high levels of utilisation of specialities allied to diabetes. There were 77.7% of older diabetic people who had seen an eye specialist within the last year and 79.9% had had their feet examined within the last year. Less people had seen a dietician within the last year (31.1%). Less emphasis is placed on annual dietician review, than annual eye and foot review, so this result was consistent with expectations.

There was a high degree of cognitive impairment, measured using the Mini Mental State Examination (MMSE), within the diabetic population, (22.5%). This compared to 15.8% in the non diabetic population. There was 22.2% of people who were taking hypoglycaemic medication who had cognitive impairment (MMSE=<23). There were 19.1% of people who had a MMSE=<23 who reported testing their blood at home.

9.2.4 Hypertension and the older diabetic person

The systolic blood pressure readings were similar in the people with and the people without diabetes. The average systolic blood pressure for people with diabetes was 149.3 mmHg compared to 148.6 mmHg in the non diabetic population. There were over 80% of people, with and without diabetes, who had systolic blood pressure above 130 mmHg.

Diastolic blood pressure was lower in people with diabetes compared to people without diabetes, 73.2 mmHg vs 74.7 mmHg. There was evidence to suggest that this may have been due to increased treatment in people with diabetes.

There were no strong and consistent associations between hypertension and diabetic complications found in this trial. These results, or lack of them, may have been a reflection of the cross sectional trial design. This point is explored further in this chapter, see section 9.3.2.

9.2.5 Renal impairment and the older diabetic person

Less strong associations between, proteinuria and raised creatinine, and diabetic endpoints were observed than may have been expected from the reviewed literature. The only association of note was observed between raised creatinine and cerebrovascular accidents in the diabetic population. Interestingly worsening GFR showed a strong association with increased macrovascular end points, although this relationship was not seen with microvascular end points. When GFR above and below 60 ml/min per 1.73 m^2 was assessed worsening GFR was associated with diabetic end points. This was particularly strong in the non diabetic group. In the non diabetic population poor vision, angina, myocardial infarction and cerebrovascular accidents were all shown to be associated with a GFR below 60 ml/min per 1.73 m^2. In the diabetic population the only associations demonstrated were between lower GFR and myocardial infarction and cerebrovascular disease.

The observational nature of the study and secondary analysis of the dataset, were potential explanations for the absence of significant results recorded.

9.2.6 Admission to hospital and the older diabetic person

Diabetes contributed to an increased rate of admission to hospital when compared to non diabetic people of similar age and sex. Rate ratio, 1.31 (95% CI, 1.23-1.39) comparing admissions in the diabetic population against the non diabetic population. Men with diabetes had a higher rate of admission to hospital than women with diabetes. Diabetic people also had a higher average number of admissions per person. The average number of admissions per person was 1.58

in the non diabetic population. The average number of admissions per diabetic person was 1.64, ($p<0.001$). Diabetic people spent longer in hospital per admission. The average length of stay was 12.4 days and 13.9 days for the non diabetic and the diabetic participants respectively ($p<0.001$).

Social deprivation, as measured by the Carstairs index, was associated with an increased odds ratio of being admitted to hospital. Current or ex-smokers, were also found to be associated with an increased odds ratio of hospital admission. Both of these factors have previously been identified as contributing to increased admission in diabetic populations.

9.2.7 Mortality and the older diabetic person

Diabetes was associated with all cause mortality in men and women, up to and including those aged over 85 years. The adjusted hazard ratio for death due to diabetes for men and women aged over 75 years was 1.50 (95% CI, 1.38-1.65). The hazard ratio remained approximately 1.50 for each age group up to 89 years. These results are in contrast to previous published results which suggest that diabetes becomes less hazardous with increasing age. It appeared that diabetes also contributed to death in people aged over 90 years, although the result was not significant. In the over 90 year age group a lack of statistical power may have been responsible for the lack of significant results.

Similarly, circulatory death rates were raised in people with diabetes. Overall the rate of death from renal causes was higher in people with diabetes than people without diabetes. Low numbers of deaths from renal causes prevented further subgroup analysis to be accurately performed.

Proteinuria and raised creatinine were associated with death (all cause, circulatory and renal) in older diabetic people. These results are in contrast to chapter 6, when only limited associations were found between diabetic end points and either of these exposure variables. The positive associations recorded reflect the statistical strengths of the MRC study; it was designed to analyse mortality outcome data not detect cross sectional observations in secondary analyses. Worsening GFR resulted in an increased hazard ratio for all cause, circulatory and renal death.

9.3 The methodology of the MRC trial and the implications for this thesis

9.3.1 The primary aim of the MRC trial

The primary aims of the MRC trial were to measure the affects of different approaches to assessment and management of older people(66;80). It was described fully in section 2.1.1. It was envisaged at the trial outset that there would be a large amount of additional data produced in the process of conducting the trial. This information was always likely to be of use to health researchers. This PhD thesis uses part of the additional data generated. It is important to state that this thesis is, therefore, a secondary analysis of the MRC trial. A primary concern of secondary analyses is "data dredging". This is the practice of simply analysing as many results, and permutations of results, as possible, in order to identify statistically significant results. This often occurs in studies where the primary hypotheses of the study has not been adequately answered. I would argue that this has not been the case in the writing of this thesis. This thesis involved the analysis of data relating the health care of the diabetic elder, testing predetermined hypotheses identified in the course of the development of this PhD. It is simply that the source of the data used in this thesis came from another trial. The results of this thesis are unconnected to the results of the original trial.

9.3.2 The design of the MRC trial

The MRC trial collected cross sectional data at the time of the detailed screening assessment. It is this information that was used for the a large amount of this thesis. Cross sectional data formed the basis of the identification and description of the diabetic population. It was used in determining the associations between diabetes, hypertension and renal impairment. As has been alluded to earlier in this thesis, this sort of observational analysis of diabetes and its complications is not ideal. It simply does not have the power or subtlety to detect differences between the populations. A cohort study would have been far more suitable. It would have had the ability to follow diabetic people with and without hypertension or renal impairment and identify any differences in the outcome of diabetic end points. The observational nature of some of the results may well have contributed to the lack of associations seen between diabetes, hypertension, renal impairment and many of the diabetic end points.

The MRC trial used a self reported questionnaire for many variables. This has epidemiological implications(304). Any responses will be subject to reporting bias. Reporting bias occurs when a trial participant reports an exposure incorrectly. This commonly occurs when a person inaccurately reports an exposure due their own attitudes, beliefs and perceptions. For example, self reporting as a non smoker to avoid being stigmatised (perceived or otherwise) as a smoker. Fortunately, we had a one method of cross checking the self reporting of diabetes, by the use of the EMIS data. The high sensitivity and specificity estimates which were calculated in this thesis, using the EMIS data show that, while not perfect, the self reporting of diabetes was reasonable. This supports the validity of the results generated in this thesis. Despite this, it was not possible to validate all the variables using EMIS data. Some of the self reported variables used in the MRC trial have previously been validated and shown to be accurate(159). However, not all of the different variables self reporting accuracy has been established. Therefore self reporting bias should be noted as a limitation of this thesis.

9.3.3 The responding participants of the MRC trial

The overall response rate for people invited to participate in the universal arm of the trial was 70.5%. This is high for a large study in this age group. It is virtually impossible to obtain 100% enrolment in a clinical trial of this kind and scale. People invited to attend may move home or die, before they are formally enrolled. Many people simply do not want to be involved in clinical trials. People may be too ill to participate. Many people are unable to find the time or the inclination to take part no matter how many times they are approached or reminded. The result is a group a trial "participants" who constitute the non responders, of which there had already been some discussion.

Chapter 8 showed that these non responding individuals have a higher mortality than responding individuals. The possible reasons for this were discussed in full in chapter 8. One of the reasons that non responders have a higher mortality than responders is the higher prevalence of all diseases in this population. It is therefore likely that the prevalence of diabetes, detected and undetected is higher, in the non responding population. This is another reason that the prevalence estimates in this thesis are likely to be an underestimation of the true figure in the community.

9.3.4 Statistical methods used in the MRC trial

The presence of missing data raises questions about any statistical inferences generated(305). The primary issue is whether the missing data constitutes different data compared to the data which is not missing. For the purposes of this thesis decisions were taken *a priori* regarding the management of missing data. Two methods were used. The first method was to ignore small amounts of missing data. The size of the MRC trial enabled small amounts of missing data not be considered because they simply would not have been large enough to meaningfully alter the results. For example, 100 missing entries constituted 0.66% of all entries when the total participating trial population of 15095 was considered. Therefore in the case of this analysis, if a variable had less than 100 missing data entries, these missing data entries were ignored. The second method of considering missing data was employed for any variable which had over 100 missing data entries. People with the missing data were treated as a separate strata and compared with the reference populations. For example, did diabetic people with proteinuria have more missing data, than non diabetic people with proteinuria. The point being to detect differences in trial subjects with missing data compared to trial subjects without missing data. In the MRC trial people with missing data were not found to be different from those without missing data for any area which was assessed. Thus, while undetected bias may still exist between those with and those without missing data, the statistical methods used in this thesis to detect any differences did not find any.

Section 2.2.1 describes cluster randomisation and why it was used in the MRC trial. The analysis used in this thesis successfully accounted for cluster sampling. Therefore the results generated from the thesis are not biased due to the inadequate consideration of clustering.

9.3.5 EMIS data

EMIS data was only available for about one third of the people included in the analysis. This information improved the quality of the results in this thesis. It was used to help find cases and provide sensitivity and specificity results. In all, 42 people were found to have diabetes from the EMIS data who otherwise would not have been identified. One can hypothesise that up to another 100 people would have been identified with diabetes if the remaining two thirds of the trial population had EMIS data available. However, this data was simply not available for the majority of the trial participants. Many GPs did not use the system and a small proportion of GP practices refused access to the information, which is their right. Nonetheless, the EMIS data was still extremely helpful.

9.3.6 The benefits of the MRC trial

The MRC trial was primarily designed and funded to investigate the affect of health care screening and subsequent management options, of detected disease, in older people. It achieved those aims(80). In order to do so, it collected vast amounts of information concerning many areas of the health and socio-economic status of the older person. Part of the legacy of the MRC trial has been the database of information it created. It continues to provide the basis for multiple publications, MSc projects and PhD theses(81;82;120;121;306-310).

The MRC trial also dedicates a full page of the universal screening questionnaire to diabetes. The questions were selected by Professor N. Chaturvedi, a renowned diabetic epidemiologist. The questions reflect careful and insightful design, within the confines of this type of epidemiological study. While it does not contain every question that could have been useful to the study of diabetes, it is still an excellent source of diabetic data.

The MRC trial was funded by, amongst others, the MRC. It was conducted using General Practices as the primary clustering unit, It utilised the MRC General Practice Research Framework (MRC GPRF) which is a collaboration of research orientated practices who help conduct different clinical trials for the MRC. Within the context of the MRC GPRF, the MRC trial of assessment and management of older people in the community, highlights the strength and organisational depth of this wonderful resource.

9.3.7 The role of chance

All analytical studies are prone to certain possible alternative explanations for the results obtained. The roles of bias and confounding have been highlighted and discussed throughout this thesis. It is therefore important to mention the role of chance. It is, of course, possible that all the statistically significant results obtained in this thesis occurred by chance. However, significance testing and the generation of p values are performed to indicate the perceived mathematical strength of a result and thus estimate the likelihood that it simply occurred by chance. In accordance with standard statistical practice, p values above 0.05 were treated as non significant. Nonetheless, a p value of 0.05 implies that one in twenty of them will be wrong. However, most of the major findings in this thesis had p values far smaller than 0.05, indicating a far lower chance of an erroneous result being presented. Thus, it is highly unlikely that the results given here occurred by chance but it is, and always will be, a possibility.

9.4 The limitations of the MRC trial and the implications for this thesis

9.4.1 Glucose measurements

One of the main drawbacks of the MRC trial from the view point of this thesis was the lack of satisfactory glucose measurements. This was disappointing from two major perspectives. The first was case ascertainment. Fasting glucose measurements would have allowed for an accurate and epidemiologically valid, diagnosis of diabetes to be made. While fasting glucose measurements tend to identify younger obese people with diabetes, they almost certainly would have identified more older people with diabetes as well(18;103;311;312). The letter of invitation to participants for take part in the MRC trial did not request participants to be fasted. Therefore it was not surprising how few fasting blood tests were completed. The MRC trial conducted over 15000 blood tests and it would have been unrealistic to have expected people to attend in a fasting state at different times of the day. From an ideal epidemiological standpoint, an OGTT should have been conducted which would have allowed the most accurate detection of diagnosed and undiagnosed diabetes possible. Unfortunately, as well as being unpleasant for any individual to undergo, it is simply not practical to perform 15000 OGTTs, in people of any age let alone the older person. Therefore incomplete diabetic case ascertainment must be noted as a limitation of every aspect of this thesis.

The second major disappointment concerning the lack of glucose measurement, was the absence of a long term measure of glucose control, such as HbA1c. This information would have provided an insight into the degree of diabetic control within our diabetic population. It would also have enabled levels of glycaemic control to have been correlated with diabetic end points to assess potential associations. Like other aspects of this thesis, some of this information would have been cross sectional and thus limited. It may therefore have suffered from a lack of power. Nonetheless, it would have been interesting to have assessed glycaemic control, especially in relation to mortality. The MRC trial did not measure HbA1c because when the trial was designed this blood test was only starting to become common place and was expensive. I am sure that if the trial was repeated today HbA1c would be included.

9.4.2 Lipid measurements

In 1994, the 4S study confirmed the benefits of treatment of abnormal lipid levels using statin medications(313). The study contained relatively small numbers of participants, although some of them were aged over 60 years. Since that time many studies have continued to expand the clinical evidence base. One of the largest and most recent was the Heart Protection Study, which included people up to the age of 80 years(314). Specific benefits were seen in the diabetic participants within the Heart Protection Study(315). While the evidence for the benefits of lowering cholesterol in older people is less than younger people, it is increasing. Many authors now support statin use in fit older people up to their 9th decade and beyond(316).

With the benefit of hindsight, lipid measurements would have been beneficial. They would almost certainly have been included as part of MRC trial if it had been performed today{Bulpitt, 2005 347 /id}. The reasons it was not done are because its importance was not as well recognised as it is today among this age group and the cost, of what was then an expensive test.

9.4.3 Drug data

The analysis of the affect of the different blood pressure lowering medications, especially ACE-Is, would have been extremely interesting. For example, did the people with diabetes who were taking an ACE-I survive longer than the diabetic people who weren't taking an ACE-I? Unfortunately this proved difficult. Analyses were attempted, the results of which were not presented due to a lack of viable results. The reasons for the lack of results was several fold. Firstly, there was a relatively low number (167, 14.2%) of diabetic people taking an ACE-I, which weakened the statistical analysis. Secondly, most of these people were also taking other blood pressure lowering drugs, which confounded the results. Thirdly, and finally, it was not possible to distinguish how much blood pressure had been lowered, if at all, from taking medication.

In order to avoid these issues it is necessary to conduct randomised controlled trials. These would allow for more appropriate study of the medications used to treat blood pressure in the older diabetic person. They would randomly and in an unbiased manner select who was given medication, unlike our trial population. Repeated blood pressure measurements could be conducted detecting the amount of effect each medication was having on blood pressure. In these scenarios, both the affect of lowering blood pressure and the beneficial effects of medications themselves can be assessed.

It was not possible to conduct any useful analysis of ARB drugs. When the MRC trial was conducted in the second half of the 1990s ARBs were uncommon drugs. They had only just become commercially available. Their clinical evidence base was not well established. Up to 15% of people develop a cough while taking an ACE-I, a common reason for discontinuing these medications. One of their primary indications when ARBs were launched was as an alternative to ACE-Is in these situations. The rarity of their use was confirmed from the MRC trial, only 12 people were recorded as taking this medication. This low figure rendered any statistical analysis redundant. It is also very likely that more older people are taking ARBs today than when trial recruitment ended in 1999, which would also have made any results defunct.

9.5 Recommendations for future research highlighted from the MRC trial

9.5.1 Publication of the results of this thesis and the NSF

The National Service Frameworks have highlighted areas of knowledge, areas of concern and made attempts to standardise medical care(4;36;37). It is therefore hoped that this thesis will further add to the available knowledge base and therefore the National Service Frameworks, ultimately leading to improved care of the older diabetic person.

It is anticipated that the following fives area will provide the basis for future publications;

The prevalence estimates of diabetes, both diagnosed and undiagnosed and all of the diabetic endpoints characterised in this thesis. Chapter 3 emphasised the paucity of even basic information in the older diabetic person and this thesis helps to further characterise the older diabetic person.

The high prevalence of cognitive impairment and the poor understanding of daily diabetic management are likely to be some of the most practical and clinically useful information generated from this thesis. Cognitive impairment is rarely considered in the diabetic clinic or General Practitioners surgery when prescribing hypoglycaemic medication or insulin. The high prevalence of cognitive impairment identified in this thesis may raise the awareness of this problem.

Hypertension and renal disease in the older diabetic person were further characterised by this thesis. Many of the results were controversial and unexpected. These unexpected results were probably due to the nature of the data and therefore erroneous. While negative results deserve publication, erroneous ones do not. In which case the results which deserve highlighting are the high prevalence of hypertension and the GFR data, which were more scientifically solid.

Hospital admission data in the diabetic older person should be of use to health planners. While some interesting factors were unavailable, this thesis demonstrated that diabetes contributed to an increased number of hospital admissions and an increased number of days spent in hospital for each admission.

The mortality estimates were also revealing and were supportive to previous findings but more expansive. The results showing that diabetes remains a serious condition into the extremes of old age. These figures were generated from one of the largest populations of older diabetic people ever assembled and studied the effect of diabetes into much older age groups than has previously been attempted. They confirm the detrimental effect of diabetes into the extremes of old age.

9.5.2 Specific issues generated from this thesis

MDRD equation

Since 1999, the MDRD equation has become the equation of choice for calculating GFR(152;154). The original study, by Levey, included people aged 50.6 years, standard deviation 12.7 years(152). Two subsequent studies have validated the use of the equation in diabetic populations(155;156). The first study using a diabetic population included 1286 people with exclusively type 1 diabetes(156). The second study in diabetic people included 160 people aged 62.2 years, standard deviation 13.7 years, range 19-83 years(155).

In the MRC trial the results of the mean GFR, generated using the MDRD, did not demonstrate any meaningful difference for older people with and without diabetes. This result is surprising because the trial participants with diabetes had higher mean creatinine levels. The MDRD equation is calculated using logarithmic manipulation of the variables of creatinine and age (it also contains fixed correction factors for gender and people of black origin). It is possible that this logarithmic manipulation becomes unreliable with increased age. The MRC trial did not precisely measure GFR and therefore it is not justified to reject the MDRD equation on the basis of this result.

Conversely, this thesis generated some results supporting the use of GFR, calculated using the MDRD equation. This thesis demonstrated that worsening GFR, either per unit change and below 60 ml/min per 1.73 m^2 predicted some diabetic end points and death; good reasons for promoting the use of GFR calculated using the MDRD equation. However, it would appear sensible to recommend that formal GFR measurements are conducted in the older person, with and without diabetes, and the MDRD equation properly validated in older populations.

Routine MMSE evaluation

The MRC trial demonstrated high levels of cognitive impairment in the diabetic population. Over one in five older people with diabetes who were taking hypoglycaemic medication had cognitive impairment. This figure is not only high but it is extremely concerning. It argues for the routine use of regular cognitive function testing in older diabetic people. In the absence of appropriate supervision of daily diabetic care, i.e. a cognitively intact primary carer, alternative treatment regimes should be considered.

Systolic BP>130 mmHg

In the MRC trial, over 80% of older people with diabetes had a systolic blood pressure above 130 mmHg. The ADA currently recommends treatment for systolic blood pressure above this level in people with diabetes(196). This recommendation applies to older people. This recommendation is the most aggressive currently used. During this thesis this lower “aggressive” figure was used as a hypothesis for the threshold of treatment benefit. The implications of treating 80% of diabetic people aged over 75 years are huge and could not be justified from the results generated in this thesis. In contrast, there are European guidelines specifically designed for the older diabetic person(39). The European guidelines suggest systolic blood pressure should not exceed 140 mmHg in fit older diabetic people and 150 mmHg in frail older diabetic people. It appears that the European guidelines are currently the most appropriate in this age group.

9.5.3 General recommendations relating to epidemiology in the older diabetic person

For nearly every aspect of this thesis there is a smaller amount of epidemiological information available compared to younger diabetic populations. Much of the evidence for diabetic management is based on extrapolation of results from younger populations. This is highlighted by the UKPDS, one of the premier type 2 diabetes trials. It enrolled people with a median age of 53 years and no people older than 65 years(14).

One of the reasons for a smaller evidence base for the older diabetic person is historical. Diabetes used to be a disease of younger people. However, for reasons that have been discussed, it is increasingly becoming a disease of older people. Therefore, the amount of known epidemiology is increasing and will continue to do so. Whether older people are beginning to be recruited into clinical trials is less clear. There is some evidence to suggest that they might be. For example, the Heart Protection Study included people up to the age of 80 years(314). Nonetheless, this still does not provide clinical evidence for people aged over 80 years. Age should not usually be a factor in deciding on inclusion in to a trial. If a trial is randomised, by definition, age should not be a factor.

The possibility that diabetes behaves differently at the extremes of age is another area of current research. There are several hypothesis, highlighted in the previous chapters, to suggest that diabetes may become less harmful with age. These include excess mortality at younger ages in susceptible individuals and a lack of time for the development of diabetic complications. Trials are underway which assess these issues..

It must be a recommendation of this thesis that an increased amount of research in to diabetes in the elderly is performed. One of the most easily accessible routes would be the inclusion of older people in clinical trials.

9.6 Conclusions

- The MRC study represents one of the largest and most varied community based resources for the study of diabetes available worldwide.
- Prevalence of diabetes and its complications are common in older people.
- Of major concern is the apparently high degree of cognitive impairment in the older diabetic person.
- Older diabetic people utilise all diabetic healthcare providers and services and are prescribed a wide range of diabetic medications.
- The prevalence of systolic hypertension was extremely high in the older diabetic population, this has major implications if all these people are to receive treatment. Hypertension and renal impairment were not strongly associated with diabetic endpoints, which were commonly seen in younger populations. This may have been the result of the inappropriate design of this study to assess these issues.

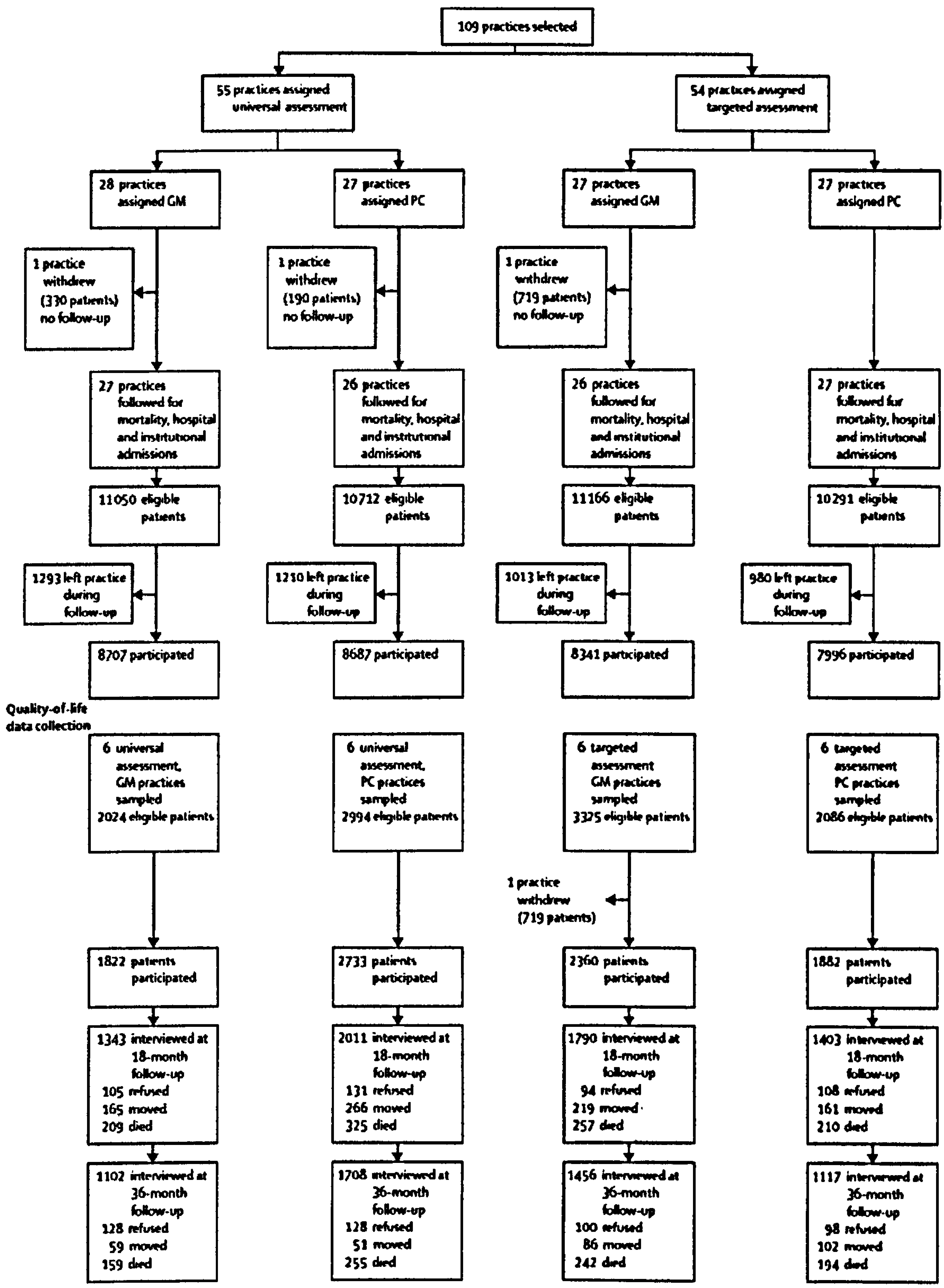
- Diabetes was clearly associated with increased admission to hospital and longer stays in hospital following admission.
- Diabetes was associated with mortality in both sexes at least up to the age of 90 years.
- Diabetes in the older person needs to be recognised as a major issue and enrolment in clinical trials should not be limited by age.

Appendices

Appendix 1.

The Design of the MRC Trial of the Assessment and Management of Older People in the Community

The design of the MRC trial is given overleaf. It includes description of the targeted arms and the universal arms of the trial. It also shows multidisciplinary geriatric care (GM) and primary care based treatment (PC). The quality of life assessment is also highlighted at the bottom of the page. Reproduced courtesy of Professor Astrid Fletcher.


109 practices selected
55 practices assigned universal assessment
54 practices assigned targeted assessment
28 practices assigned GM
27 practices assigned PC
27 practices assigned GM
27 practices assigned PC
1 practice withdrew (330 patients) no follow-up
1 practice withdrew (190 patients) no follow-up
1 practice withdrew (719 patients) no follow-up
27 practices followed for mortality, hospital and institutional admissions
26 practices followed for mortality, hospital and institutional admissions
26 practices followed for mortality, hospital and institutional admissions
27 practices followed for mortality, hospital and institutional admissions
11050 eligible patients
10712 eligible patients
11166 eligible patients
10291 eligible patients
1293 left practice during follow-up
1210 left practice during follow-up
1013 left practice during follow-up
980 left practice during follow-up
8707 participated
8687 participated
8341 participated
7996 participated
Quality-of-life data collection
6 universal assessment, GM practices sampled 2024 eligible patients
6 universal assessment, PC practices sampled 2994 eligible patients
6 targeted assessment GM practices sampled 3325 eligible patients
6 targeted assessment PC practices sampled 2086 eligible patients
1 practice withdrew (719 patients)
1822 patients participated
2733 patients participated
2360 patients participated
1882 patients participated
1343 interviewed at 18-month follow-up 105 refused 165 moved 209 died
2011 interviewed at 18-month follow-up 131 refused 266 moved 325 died
1790 interviewed at 18-month follow-up 94 refused 219 moved 257 died
1403 interviewed at 18-month follow-up 108 refused 161 moved 210 died
1102 interviewed at 36-month follow-up 128 refused 59 moved 159 died
1708 interviewed at 36-month follow-up 128 refused 51 moved 255 died
1456 interviewed at 36-month follow-up 100 refused 86 moved 242 died
1117 interviewed at 36-month follow-up 98 refused 102 moved 194 died

Appendix 2.

The detailed questionnaire

The following pages contain an exact reproduction of the detailed questionnaire. The page numbers here represent the page numbers which have been highlighted throughout the text in relation to this appendix.

MRC ASSESSMENT OF ELDERLY PEOPLE IN GENERAL PRACTICE

DETAILED ASSESSMENT

Patient Name Label

Barcode Label

Date of birth

Day: 0 1 2 3 / 4 5 6 7 8 9

Month: 0 1 2 3 4 5 6 7 8 9 10 11 12

Year: 0 1 2 3 4 5 6 7 8 9

Sex: Male ☐ Female ☐

Marital status

- ☐ Single
- ☐ Married
- ☐ Separated/divorced
- ☐ Widowed
- ☐ Living with a partner

PLEASE TICK APPROPRIATE BOX:-

- ☐ Interview completed with subject
- ☐ Totally proxy interview *(Reasons for proxy)*
- ☐ Partly proxy interview *(Reasons for proxy)*
- ☐ Subject unable to complete interview *(No proxy)*
- ☐ Subject not found *(Reason not found)*
- ☐ Subject refused interview
- ☐ Subject died
- ☐ Subject moved to long stay care
- ☐ Subject admitted to hospital
- ☐ Subject moved away *(New address)*
  (New GP/FHSA)

Nurse number: 0 1 2 3 4 5 6 7 8 9 (10, 1)

Nurse name

Date of interview

Day: 0 1 2 3 / 4 5 6 7 8 9

Month: 0 1 2 3 4 5 6 7 8 9 10 11 12

Year: 0 1 2 3 4 5 6 7 8 9

Place of interview

- Surgery ☐
- Residential home ☐
- Own home ☐
- Other *(Specify)* ☐

Visit start time *(use 24 hour clock)*

Hours: 0 1 2 / 3 4 5 6 7 8 9

Minutes: 0 1 2 3 4 5 / 6 7 8 9

Interview start time *(use 24 hour clock)*

Hours: 0 1 2 / 3 4 5 6 7 8 9

Minutes: 0 1 2 3 4 5 / 6 7 8 9

After 3 minutes rest, take the patient's sitting blood pressure. Repeat sitting blood pressure after another 3 minutes rest, and then take standing blood pressure after 3 minutes rest.

Record to the nearest 2mmHg.

	Sitting First	Sitting Second	Average corrected sitting reading		Standing
Systolic	☐☐☐	☐☐☐	True Systolic	☐☐☐	☐☐☐
Diastolic	☐☐☐	☐☐☐	True Diastolic	☐☐☐	☐☐☐
Zero error	☐☐	☐☐			☐☐

Calculations

Action:
Repeat in 1 week if average sitting systolic is >=180mmHg, or average sitting diastolic is >=100mmHg. To repeat for either, standing systolic must be >=140mmHg.

Repeat blood pressure:

	Sitting First	Sitting Second	Average corrected sitting reading		Standing
Systolic	☐☐☐	☐☐☐	True Systolic	☐☐☐	☐☐☐
Diastolic	☐☐☐	☐☐☐	True Diastolic	☐☐☐	☐☐☐
Zero error	☐☐	☐☐			☐☐

Calculations

Immediate Action:
(Any age) If average repeat sitting systolic >=220mmHg or sitting diastolic >=115mmHg, inform GP within 4 hours.

Action:
Refer to team if subject is less than 80 years old and average repeat sitting systolic >=180mmHg or sitting diastolic >=100mmHg. To refer for either, standing systolic pressure must be >=140mmHg.

2(a) Pulse rate

	0	1	2	3	4	5	6	7	8	9
100										
10										
1										

Immediate Action:
If pulse <40 or >130, inform GP within 4 hours.

Action:
Refer to team if pulse 40-49 or 110-129.

2(b) Continuously irregular pulse? Yes ☐ No ☐

Action:
If yes, do ECG if surgery has facilities. Refer to team if ECG reports atrial fibrillation, atrial flutter or runs of ventricular extrasystoles. If surgery has no ECG facility, refer to team.

3 Measure patient's standing height to the nearest 0.1cm.

	0	1	2	3	4	5	6	7	8	9
100										
10										
1										
0.1										

cm

4 Measure patient's weight without coat and shoes to the nearest 0.1 kilogram.

	0	1	2	3	4	5	6	7	8	9
100										
10										
1										
0.1										

Kg

5(a) Measure patient's demi span to nearest 0.1cm.

	0	1	2	3	4	5	6	7	8	9
100										
10										
1										
0.1										

cm

5(b) Repeat demi span measurement to nearest 0.1cm.

	0	1	2	3	4	5	6	7	8	9
100										
10										
1										
0.1										

cm

6(a) Measure patient's mid-arm circumference to nearest 0.1cm.

	0	1	2	3	4	5	6	7	8	9
10										
1										
0.1										

cm

6(b) Repeat mid-arm circumference measurement to nearest 0.1cm.

	0	1	2	3	4	5	6	7	8	9
10										
1										
0.1										

cm

'(a) Measure patient's waist circumference to nearest 0.1cm.

	0	1	2	3	4	5	6	7	8	9
100										
10										
1										
0.1										

cm

'(b) Repeat waist circumference measurement to nearest 0.1cm.

	0	1	2	3	4	5	6	7	8	9
100										
10										
1										
0.1										

cm

3(a) Measure patient's hip circumference to nearest 0.1cm.

	0	1	2	3	4	5	6	7	8	9
100										
10										
1										
0.1										

cm

3(b) Repeat hip circumference measurement to nearest 0.1cm.

	0	1	2	3	4	5	6	7	8	9
100										
10										
1										
0.1										

cm

Please indicate if there were any special circumstances that might have affected any of the above anthropometric measurements. Yes ☐ No ☐

Please record these special circumstances in the space below, (see training notes).

"I am now going to ask you some questions about your recent health, that is, over the past month."

9(a) *Have you ever had any pain or discomfort in your chest?*
Yes ☐
No ☐ ←go to (i)

9(b) *Do you get this pain or discomfort when you walk uphill or hurry?*
Yes ☐
No ☐ ←go to (i)

9(c) *Do you get it when you walk at an ordinary pace on the level?*
Yes ☐
No ☐

9(d) *When you get any pain or discomfort in your chest, what do you do?*
Stop ☐
Slow down ☐
Continue at the same pace ☐ ←go to (i)

9(e) *Does it go away when you stand still?*
Yes ☐
No ☐ ←go to (i)

9(f) *How soon?*
10 minutes or less ☐
More than 10 minutes ☐ ←go to (i)

9(g) *Where do you get this pain or discomfort?* (Tick all places mentioned)

	Yes	No
Sternum	☐	☐
Left chest	☐	☐
Left arm	☐	☐
Other	☐	☐

If "other", specify ☐

9(h) *Are you receiving treatment for this?*
Yes ☐
No ☐

Action: If No, refer to team

9(i) *Have you ever had a severe pain across the front of your chest lasting for half an hour or more*
Yes ☐
No ☐

10(a) *Are you wearing a hearing aid now?*
Yes ☐ ←go to (c)
No ☐

10(b) *Do you have a hearing aid at home for your own use?*
Yes ☐
No ☐ ←go to (e)

10(c) *Do you use the hearing aid regularly?*
Yes ☐
No ☐

10(d) *Does it help?* A lot ☐ A little ☐ Not at all ☐

Only ask (e) if "No" to (a) and (b). Otherwise go to Q11.

10(e) *Have you ever tried one?*
Yes ☐
No ☐ ←go to 11

10(f) *Did it help?* A lot ☐ A little ☐ Not at all ☐

11 *"I am now going to do some checks on your hearing by whispering some letters and numbers. Please keep looking forward".*

Stand behind subject at a distance of 6 inches. Take a deep breath in, breathe right out and then whisp at one item per second: *"3,A,2"*. Ask the subject to repeat this. The test is passed if the sequence is repeated correctly. If they respond incorrectly or not at all, the test is repeated once more using *"1,F,5*

Passed first time ☐ Passed second time ☐ Failed ☐

Action:
If patient fails, examine the ears.

Examination of the ears

Nothing abnormal ☐

Wax ☐

Other (specify) ☐

Action:
If wax not present and hearing has not been investigated in the last year, refer for audiometry. If wax is present, arrange for drops and syringing. Repeat whispered voice test 1 week after syringing.

Repeat whispered voice test.

Date

Day	0	1	2	3									
	0	1	2	3	4	5	6	7	8	9			
Month	0	1	2	3	4	5	6	7	8	9	10	11	12
Year	0	1	2	3	4	5	6	7	8	9			

Passed first time ☐ Passed second time ☐ Failed ☐

Action:
If patient still fails and hearing has not been investigated in the last year, refer for audiometry.

12 *"As people grow older it is quite normal to find they sometimes have trouble with their bladder or bowels. I'd like to ask you some questions about it."*

12(a) **Ask all:** *Do you ever wet yourself if you are not able to get to the toilet as soon as you need to, or when asleep, or if you cough or sneeze?*

- Yes ☐
- No ☐ ←go to 13
- Catheter ☐ ←go to (d)

12(b) **If yes,** *how often does this happen?*

- More than once a day ☐ *
- Once a day ☐ *
- Three or more times a week ☐ *
- Once or twice a week ☐ *
- Less than once a week ☐

12(c) **If yes,** *is it just a few drops or more than that?*

- Just a few drops ☐
- More than that ☐ *

Action: If *incontinent of urine (more than a few drops) once a week or more, do MSU. If infected MSU refer to team; if not infected refer to continence advisor/community nurse.

12(d) **If catheter,** *do you have any problems with this?*

- Yes ☐
- No ☐

Action: If yes, refer to continence advisor/community nurse

13(a) **Ask all**: *Do you ever soil or mess yourself?*

Yes ☐
No ☐ ←go to 14

13(b) **If yes,** *how often do you have soiling accidents?*

More than once or twice a day ☐ *
Once or twice a day ☐ *
Three or more times a week ☐ *
Once or twice a week ☐ *
Once or twice a month ☐
Less than once a month ☐

Action: If 3 or more times a week, refer to team. If once or twice a week, refer to continence advisor/ community nurse.

14 **Men only, women go to Q15.**

14(a) ***In the <u>last month</u> have you usually had to get up to pass water during the night?***

Yes ☐
No ☐ ←go to (d)

14(b) **If yes,** *how often per night?* 0 1 2 3 4 5 6 7 8 9 ☐☐☐☐☐☐☐☐☐☐ 1 times:

Twice a night or less - go to (d)
More than twice - go to (c)

14(c) **If more than twice,** *have you seen your doctor about this problem in the last month?*

Yes ☐
No ☐

Action: If No, refer to team.

14(d) ***In the <u>last month</u> have you had difficulty in passing your water?***

No difficulty ☐ ←go to 16
Some difficulty ☐ ←go to 16
A lot of difficulty ☐ *

14(e) **If a lot of difficulty,** *have you seen your doctor about this problem in the last month?*

Yes ☐
No ☐

Action: If a lot of difficulty passing water **<u>and</u>** not seen doctor in the last month, refer to team.

Women only. Men go to 16.

15a *How old were you when you had your first menstrual period?* 0 1 2 3 4 5 6 7 8 9 ☐☐☐☐☐☐☐☐☐☐ 10 ☐☐☐☐☐☐☐☐☐☐ 1 years

15b *How old were you when you had your last menstrual period?* 0 1 2 3 4 5 6 7 8 9 ☐☐☐☐☐☐☐☐☐☐ 10 ☐☐☐☐☐☐☐☐☐☐ 1 years

15c *Did your periods stop naturally, because of surgery, or for some other reason?*

Naturally ☐
Surgery ☐
Other (specify) ☐ ←

15d *Have you ever been pregnant (including miscarriages and stillbirths)?*

Yes ☐
No ☐ ←go to 16

15e *How many children, including stillbirths, have you had?* 0 1 2 3 4 5 6 7 8 9 ☐☐☐☐☐☐☐☐☐☐ 10 ☐☐☐☐☐☐☐☐☐☐ 1

16	**Ask all patients:**			
16(a)	*In the __last month__ have you been more constipated than usual?*	Yes No	☐ ☐	 ←go to 17
16(b)	**If yes,** *have you seen your doctor about this in the last month?*	Yes No	☐ ☐	←go to 17
16(c)	**If no,** *is it a problem for you?*	Yes No	☐ ☐	
	__Action:__ If it is a problem, refer to team			
17(a)	*In the __last month__ have you had repeated attacks of diarrhoea?*	Yes No	☐ ☐	 ←go to 18
17(b)	**If yes,** *have you seen your doctor about this in the last month?*	Yes No	☐ ☐	←go to 18
17(c)	**If no,** *is it a problem for you?*	Yes No	☐ ☐	
	__Action:__ If it is a problem, refer to team			
18	*In the __last month__ have you had alternating attacks of diarrhoea and constipation?*	Yes No	☐ ☐	
19(a)	*In the __last month__ have you had blood in your motions?*	Yes No	☐ ☐	 ←go to 20
19(b)	**If yes,** *have you seen your doctor about this in the last month?*	Yes No	☐ ☐	
	__Action:__ If No, send stool specimen to laboratory for analysis. If it is positive for blood, refer to team			
20(a)	*In the __last month__ have your motions been black?*	Yes No	☐ ☐	 ←go to 21
20(b)	*Are you taking iron tablets?*	Yes No	☐ ☐	←go to 21
20(c)	**If no,** *have you seen your doctor about this in the last month?*	Yes No	☐ ☐	
	__Action:__ If No, send stool specimen to laboratory for analysis. If it is positive for blood refer to team			
21	*Can you chew satisfactorily?*	Yes No	☐ ☐	
	__Action:__ If No, refer to dentist.			
22(a)	*Do you have a problem with swallowing?*	Yes No	☐ ☐	 ←go to 23
22(b)	**If yes,** *have you seen your doctor about this?*	Yes No	☐ ☐	
	__Action:__ If No, refer to team.			
23(a)	*In the __last month__ have you vomited blood or vomit that looks like coffee grounds?*	Yes No	☐ ☐	 ←go to 24
23(b)	**If yes,** *have you seen your doctor about this in the last month?*	Yes No	☐ ☐	
	__Action:__ If No, refer to team.			

24(a)	*Have you coughed up blood?*	Yes ☐ No ☐ ←go to 25	
24(b)	**If yes,** *have you seen your doctor about this in the last month?*	Yes ☐ No ☐	

Action: If No, refer to team.

25(a)	*Do you **usually** bring up any phlegm from your chest first thing in the morning in the winter?*	Yes ☐ No ☐
25(b)	*Do you **usually** bring up any phlegm from your chest during the day - or at night - in the winter?*	Yes ☐ No ☐

If Yes to 25(a) or 25(b), ask 25(c). If not, go to 25(d).

25(c)	*Do you bring up phlegm like this on most days for as much as three months each year?*	Yes ☐ No ☐
25(d)	*In the past three years, have you had a period of increased cough and phlegm lasting for three weeks or more?*	Yes ☐ ←one period Yes ☐ ←2 or more periods No ☐
25(e)	*Does your chest sound wheezy or whistling on most days (or nights)?*	Yes ☐ No ☐
25(f)	*Do you get short of breath walking with people of your own age on level ground?*	Yes ☐ No ☐
25(g)	*Are you short of breath on talking?*	Yes ☐ No ☐ ←go to 26
25(h)	**If yes to Q25(g),** *have you seen your doctor about this in the last month?*	Yes ☐ No ☐

Action: If No, refer to team.

26(a)	*Do you have swelling of your legs up to your knees on getting up in the morning?*	Yes ☐ No ☐ ←go to 27
26(b)	**If yes,** *have you seen your doctor about this in the last month?*	Yes ☐ No ☐

Action: If No, refer to team.

27	*In the last **six months**, how many falls have you had **at home**?*	None ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ More than 4 ☐

Action: More than 4, refer to team

28	*Over the last **six months** have you noticed unexplained weight loss of more than half a stone?*	Yes ☐ No ☐

Action: If Yes, refer to team.

29 *Compared with other people of your own age would you say that your health is generally: excellent, good, fair or poor?*

- Excellent ☐
- Very good ☐
- Good ☐
- Fair ☐
- Poor ☐

30 *Compared to other people of your age, would you describe yourself as:*

- Very physically active ☐
- Fairly physically active ☐
- Not very physically active ☐
- Not at all physically active ☐

31 Here are some activities which people sometimes find difficult. For each one ask, "Do you do the following by yourself or could you do the following by yourself if you had to? And if unable to do it alone, do you receive enough help?"

		No difficulty	Some difficulty	Unable to do it alone but help is usually available	Unable to do it alone and not enough help is available
31a	Cut your own toe nails	☐	☐	☐	☐ *
31b	Dress yourself including zips or buttons	☐	☐	☐	☐ *
31c	Cook a hot meal	☐	☐	☐	☐ *
31d	Do light housework or simple repairs	☐	☐	☐	☐ *
31e	Go up and down stairs and steps (if necessary using a frame, tripod or stick)	☐	☐	☐	☐
31f	Wash all over (including bathing or showering)	☐	☐	☐	☐ *
31g	Walk 50 yards down the road (if necessary using a frame, tripod or stick)	☐	☐	☐	☐
31h	Do shopping	☐	☐	☐	☐ *

Action: Any * refer to the appropriate service.

Introduction:
I am now going to ask you some questions which involve memory, reading and writing type exercises.
Nurse Instruction:
Remember not to prompt the patient. Ask the questions exactly as they are written.

32 **Orientation** (Ask the following questions)

			Correct	Incorrect
32a	*What is the date today? Code whether date, month and year are correct).*	Date	☐	☐
32b		Year	☐	☐
32c		Month	☐	☐
32d	*What day of the week is it today?*	Day	☐	☐
32e	*What is the season?*	Season	☐	☐

(Seasons:
(Jan/Feb = Winter
(March = Winter or Spring
(Apr/May = Spring
(June = Spring or Summer
(July/Aug = Summer
(Sept = Summer or Autumn
(October = Autumn
(Nov/Dec = Autumn or Winter

			Correct	Incorrect
32f	*What is the name of this place? Where is it located?* For home visits ask, *"What is the full address of this place?"*	Place	☐	☐
32g	*What floor of this building are we on?*	Floor	☐	☐
32h	*What is the name of this city/town/village?*	Town	☐	☐
32i	*What county are we in?*	County	☐	☐
32j	*What country are we in?*	Country	☐	☐

33 **Immediate Recall**

Instruction to Patient:
"I am now going to say three words. After I have finished saying all three, I want you to repeat them. Remember what they are because I am going to ask you to name them in a few minutes.

Name these three objects taking 1 second to say each:

"Apple" "Table" "Penny"

Rate the first attempt. If any errors or omissions are made on the first attempt, repeat all the names until patient learns all three up to a maximum of 5 repeats.

First Repetition

	Correct	Incorrect
Apple	☐	☐
Table	☐	☐
Penny	☐	☐

34 **Attention and Calculation**

34a *"Now I would like you to take 7 away from 100".*
"Now take 7 away from the number you get".
"Now keep taking 7 away until I tell you to stop".

Rate as correct each time the difference is 7, even if a previous answer was incorrect. Do not repeat the number you were given.

	Correct	Incorrect
Subtraction 1	☐	☐
2	☐	☐
3	☐	☐
4	☐	☐
5	☐	☐

34b **If 34a is not done, ask 34b.**
NB Only count score for 34b if 34a not done.

Ask the subject to spell the word "world" backwards
The score is the number of letters in correct position.
For example, "dlrow" is 5, "dlorw" is 3.

	Correct	Incorrect
d		
l		
r		
o		
w		

35 **Recall**

"What were the three words I asked you to repeat a little while ago?" (33).

	Correct	Incorrect
Apple		
Table		
Penny		

36 **Language**

"Now I am going to ask you to do some things, so please listen carefully. Some may seem very simple, but please bear with us."

If, for physical or educational reasons, the patient is not able to complete this section, leave all coding boxes blank and make a note of the reasons for omission. Then go to the end of this section (Deriving total score).

36a **Naming**

Show the subject a wrist watch and ask, *"What is this called?"*

Show a pencil and ask, *"What is this called?"*

Answer is only correct if object is accurately named.

	Correct	Incorrect
Watch		
Pencil		

36b **Repetition**

*"I am now going to say something and I would like you to repeat it after me": **"No ifs, ands, or buts"**.*
Only one presentation is allowed, so it is essential that you read the phrase clearly and slowly, enunciating all the s's.

	Correct	Incorrect
Repetition		

36c **3-Stage command**

"I am now going to give you a piece of paper. When I do, take the paper in your RIGHT hand, fold the paper in half with BOTH hands and put the paper down on your LAP".
Hand the paper to the patient's midline.

If the full sequence is not completed, repeat the whole instruction.

	Correct	Incorrect
Takes paper in right hand		
Folds paper in half		
Puts paper on lap		

36d **Reading**

Hold up the card which reads **"Close your eyes"**, so the subject can see it clearly. Say, *"Please read what is here and do what it says".*

Score as correct only if patient actually closes eyes.

	Correct	Incorrect
Closes eyes		

Writing

36e Give the subject a blank piece of paper and say, *"Write a complete sentence on the piece of paper"*. Spelling and grammar are not important. The sentence must have a subject and a verb.

	Correct	Incorrect
Writes sentence	☐	☐

Copying

36f *"Here is a drawing. Please copy the drawing on the paper"*. Give intersecting pentagons card.

Answer is correct if the two five-sided figures intersect to form a four-sided figure and if all the angles in the five-sided figures are preserved.

	Correct	Incorrect
Draws pentagons	☐	☐

Deriving total score

	Yes	No
Language section (Q36) completed:	☐	☐

Total score:

	0	1	2	3	4	5	6	7	8	9
10	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
1	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

a. For patients who did not complete the language section on physical/educational grounds, tick "No" for "language section completed".
Give one point for every correct answer and fill in the number grid.

NB **Only include scores for Q28b (world spelled backwards) if Q28a (subtraction) not conducted.**

Action: If the total score is less than 12, refer to the Community Psychiatric Nurse or Memory Clinic.

b. For all other patients, tick "Yes" for "language section completed". Sum the total of correct answers and fill in the number grid.

NB **Only include scores for Q28b (world spelled backwards) if Q28a (subtraction) not conducted.**

Action: If the total score is less than 17, refer to the Community Psychiatric Nurse or Memory Clinic.

Comments on MMSE (Q32-36):

37 *Has a doctor ever told you that you had any of the following? If yes, was that in the last year?*

	No	Yes, within last year	Yes but before last year
Pneumonia	☐	☐	☐
Emphysema	☐	☐	☐
Asthma	☐	☐	☐
Arthritis/Rheumatism	☐	☐	☐
Eczema	☐	☐	☐
Stomach ulcer/other digestive ulcer	☐	☐	☐
Haemorrhoids or piles	☐	☐	☐
High blood pressure	☐	☐	☐
Heart attack	☐	☐	☐
Stroke	☐	☐	☐
Leg ulcer	☐	☐	☐
Varicose veins	☐	☐	☐
Gout	☐	☐	☐
Depression needing treatment	☐	☐	☐
Thyroid trouble	☐	☐	☐
Cataract	☐	☐	☐
Glaucoma	☐	☐	☐
Fractured spine	☐	☐	☐
Fractured hip	☐	☐	☐
Parkinson's disease	☐	☐	☐
Cancer (if yes, ask where)	☐	☐	☐ ←Site
Infection in bladder or kidneys	☐	☐	☐
Men only			
Trouble with your prostate gland	☐	☐	☐

38a *Have you ever been told by a doctor that you have sugar diabetes?* Yes ☐ No ☐ go to 39

38b *When were you first told you had diabetes? (give year)* 19 [0 1 2 3 4 5 6 7 8 9] 10 / 1

38c *What treatment are you on for your diabetes?* (Tick all that apply)
- Diet alone ☐
- Tablets ☐
- Insulin injections ☐
- No treatment ☐

38d *Do you test your blood for sugar?* Yes ☐ No ☐

If yes, ask *"how often do you do this?"*
- About once a day ☐
- About once a week ☐
- About once a month ☐
- Less than once a month ☐

38e *Do you test your urine for sugar?* Yes ☐ No ☐

If yes, ask *"how often do you do this?"*
- About once a day ☐
- About once a week ☐
- About once a month ☐
- Less than once a month ☐

38f *Who do you normally see about your diabetes?* (Can be more than one person)
- Family doctor/GP ☐
- Hospital doctor ☐
- Practice/District nurse ☐
- No one ☐

38g *In the last year, have you had your feet examined?* Yes ☐ No ☐ D/K ☐

38h *In the last year, have you had your eyes examined?* Yes ☐ No ☐ D/K ☐

38i *In the last year, have you discussed your diet with a dietician?* Yes ☐ No ☐ D/K ☐

Nurse instruction:
Questions (j) and (m) should be asked **only to patients on tablets or insulin.**

38j *Have you ever had a low blood sugar (a "Hypo")* Yes ☐ No ☐ D/K ☐

Ask all patients on tablets or insulin Q38k to m.

38k *If you have a low blood sugar, should you increase your diabetes treatment?* Yes ☐ No ☐ D/K ☐

38l *If you have a low blood sugar, should you take a sugary drink or snack?* Yes ☐ No ☐ D/K ☐

38m *If you have the 'flu, should you stop taking your diabetes tablets/insulin?* Yes ☐ No ☐ D/K ☐

39a *I would like to ask you some questions about your housing.*

Who do you live with?

- Alone ☐
- Spouse ☐
- Son/Daughter ☐
- Other relative ☐
- Friend ☐
- Other (specify) ☐ ☐

39b *What kind of accommodation do you live in?*

- Council rental ☐
- Private rental ☐
- Housing Association ☐
- Home owner ☐
- Sheltered accommodation ☐)
- Local Authority residential home ☐)
- Private residential home ☐) go to 40
- Local Authority nursing home ☐)
- Private nursing home ☐)

If living in own or rented accommodation, ask:

		Yes	No	
39c	*In the last year have you had difficulty keeping your home warm?*	* ☐	☐	
39d	*Do you have central heating?*	☐	☐	

			All	Some	None
39e	If yes, *in which rooms?*	Living rooms	☐	☐	☐
		Bedrooms	☐	☐	☐

		Yes	No
39f	*Do you have an indoor toilet?*	☐	☐ *
39g	*Do you have a relative, neighbour or friend whom you can call on for help when required?*	☐	☐ *
39h	*Is there anyone available if you need help at night?*	☐	☐ *

__Action:__ If 3 or more *, refer to Social Services.

40a *When you need to talk about private matters or when you are worried or stressed, who can you really count on or feel at ease with?* (May give more than one answer).

- No one ☐ *
- Spouse ☐
- Friend ☐
- Neighbour ☐
- Relative ☐
- Home Help/other paid help ☐
- Warden ☐

40b *During the last year have you experienced?* (May give more than one answer)

	*Yes	No
Death or separation from a loved one	☐	☐
Serious illness in a loved one	☐	☐
Moving your residence	☐	☐

		Yes	No
40c	*Do you ever have difficulty in making ends meet, I mean, is it difficult to find the money to pay your bills?*	* ☐	☐
40d	*Do you have difficulty in managing your own finances, I mean things like paying for bills, working out change etc?*	* ☐	☐

__Action:__ If 2 or more *, refer to Social Services.

41 *I am now going to ask you some questions about how you've been feeling over the <u>past few weeks.</u> For each question, please choose the answer that best applies to you.*

		Not at all	No more than usual	Rather more than usual	Much more than usual
41a	*Have you lost much sleep over worry?*	☐	☐	☐	☐
41b	*Have you had difficulty in staying asleep once you are off?*	☐	☐	☐	☐
41c	*Have you felt constantly under strain?*	☐	☐	☐	☐
41d	*Have you been getting edgy and bad-tempered?*	☐	☐	☐	☐
41e	*Have you been getting scared or panicky for no good reason?*	☐	☐	☐	☐
41f	*Have you found everything getting on top of you?*	☐	☐	☐	☐
41g	*Have you been feeling nervous and strung-up all the time?*	☐	☐	☐	☐

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42 ***These questions are about how you've been feeling over the <u>last week.</u> For each question, please choose the answer that best applies to you.***

		Yes	No
42a	*Are you basically satisfied with your life?*	☐	☐ *
42b	*Have you dropped many of your activities and interests?*	* ☐	☐
42c	*Do you feel that your life is empty?*	* ☐	☐
42d	*Do you often get bored?*	* ☐	☐
42e	*Are you in good spirits most of the time?*	☐	☐ *
42f	*Are you afraid that something bad is going to happen to you?*	* ☐	☐
42g	*Do you feel happy most of the time?*	☐	☐ *
42h	*Do you often feel helpless?*	* ☐	☐
42i	*Do you prefer to stay at home rather than going out and doing new things?*	* ☐	☐
42j	*Do you feel you have more problems with memory than most?*	* ☐	☐
42k	*Do you think it is wonderful to be alive now?*	☐	☐ *
42l	*Do you feel pretty worthless the way you are now?*	* ☐	☐
42m	*Do you feel full of energy?*	☐	☐ *
42n	*Do you feel that your situation is hopeless?*	* ☐	☐
42o	*Do you think that most people are better off than you are?*	* ☐	☐

42p Count the number of asterisked replies:
If score is 7 or less, go to 43.

Total Score:

	0	1	2	3	4	5	6	7	8	9
10	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
1	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

If score is more than 7, ask:

42q *Are you receiving treatment for these feelings?* Yes ☐ No ☐ ←go to 42s

42r *How long have you been having this treatment* For more than 6 months ☐ 6 months or less ☐

42s **<u>Action:</u>**
Refer to team if score more than 7 <u>**and**</u> no treatment <u>**or**</u> more than 6 months on present treatment.

43a	*Do you smoke cigarettes (including hand rolled) at present?*	Yes ☐ No ☐	←go to (c)
43b	*How many cigarettes do you smoke a day?*	0 1 2 3 4 5 6 7 8 9 (10) (1)	Cigarettes go to (f)
	or how many ozs of tobacco do you smoke a day?	0 1 2 3 4 5 6 7 8 9 (1) (0.1)	Ozs of tobacco go to (f)
43c	**If current non-smoker** ask, *have you ever smoked cigarettes?*	Yes ☐ No ☐	←go to 44
43d	*How many cigarettes did you smoke a day?*	0 1 2 3 4 5 6 7 8 9 (10) (1)	Cigarettes
	or how many ozs of tobacco did you smoke a day?	0 1 2 3 4 5 6 7 8 9 (1) (0.1)	Ozs of tobacco
43e	*How old were you when you stopped smoking?*	0 1 2 3 4 5 6 7 8 9 (10) (1)	Years
	Ask all current and ex-smokers:		
43f	*How old were you when you started smoking?*	0 1 2 3 4 5 6 7 8 9 (10) (1)	Years
44a	*During the last year have you taken an alcoholic drink?*	Yes ☐ No ☐	←go to (f)

44b *During the past week how many drinks have you had of each of the following?*

Record number, including zero.

44b	Spirits - number of singles	0 1 2 3 4 5 6 7 8 9 (10) (1)
44c	Wine, Sherry or Port - number of glasses	0 1 2 3 4 5 6 7 8 9 (10) (1)
44d	Beer - number of half pints	0 1 2 3 4 5 6 7 8 9 (10) (1)

44e *Compared with 5 years ago, would you say that on the whole you drink more, less, or about the same nowadays?*

- More nowadays ☐
- Less nowadays ☐
- About the same ☐

44f **If a non-drinker** ask, *have you always been a non-drinker or did you stop drinking for some reason?*

- Always a non-drinker ☐ ←go to 45
- Used to drink but stopped ☐

44g **If stopped drinking,** *why did you stop?* (Tick all that apply)

	Yes	No
Illness, doctor's advice	☐	☐
Concerned about health	☐	☐
Too expensive	☐	☐
Other	☐	☐

If "Other", please specify: ____________________

45a *Do you have any problems with your eyesight?* Yes ☐ No ☐

45b *Do you wear glasses?* Yes ☐ No ☐ ←go to (c)
(If patient is wearing glasses, don't ask, just tick)

45c **If yes,** *do you wear them all the time, for reading only or other reason?*
Wears glasses all the time ☐
Wears glasses for reading only ☐
Other, please specify ☐ ←

45d *Are you registered as blind or partially sighted?*
Blind ☐
Partially sighted ☐
No ☐

46 **Visual Acuity**

Test with patient wearing usual glasses. Using Glasgow chart, measure the patient's vision at 3 metres. I the patient cannot see the biggest letters, then measure at 1 metre. Measure both eyes first, then each ey separately. Scores can be plus or minus. The greater the score, the worse the vision.

46a **Both eyes** / **Left eye** / **Right eye**

Plus ☐ Minus ☐ (each eye column)

0 1 2 3 4 5 6 7 8 9
1
0.1
0.01
0.001

Measured at 3 metres ☐
Measured at 1 metre ☐
Unable to read at 1 metre ☐

If a minus score, or score less than 0.5, go to Q47, If score is 0.5 or greater, re-test using pinhole.

46b **Pinhole score:** **Left eye** / **Right eye**

Plus ☐ Minus ☐ (each eye column)

0 1 2 3 4 5 6 7 8 9
1
0.1
0.01
0.001

Measured at 3 metres ☐
Measured at 1 metre ☐
Unable to read at 1 metre ☐

Action:
If pinhole score improves to less than 0.5, refer to the optician.
If pinhole score is 0.5 or more, ask if investigated in the last year: → Yes ☐ No ☐
If No, refer to ophthalmologist.

47a *Do you have any leg or foot ulcers?* Yes ☐ No ☐ ←go to 48

47b *Are they/Is it being treated?* Yes ☐ No ☐

47c *Are they/Is it healing alright?* Yes ☐ No ☐

Action:
If ulcer(s) not treated or not healing with present treatment, refer to Community Nursing services.

48a *Do you have any other problems with your feet?* Yes ☐ No ☐ ←go to 49

48b **If yes,** examine feet and specify:
(Tick all that apply)

	Yes	No
Bunions	☐	☐
Corns	☐	☐
Ingrowing toe nail	☐	☐
Very long toenails	☐	☐
Other problem	☐	☐

If "Other problem", please specify ☐

48c **If yes,** *are you receiving chiropody?* Yes ☐ No ☐

Action: If no, refer for chiropody.

49a *Do you have any ulcers or sores anywhere on your body?* Yes ☐ No ☐ ←go to 50

49b **If yes,** examine for pressure sores and record if present:

	Yes	No
Sacrum	☐	☐
Buttock	☐	☐
Heel	☐	☐
Other	☐	☐

If "Other", please specify ☐

49c *Are they/Is it being treated?* Yes ☐ No ☐

49d *Are they/Is it healing alright?* Yes ☐ No ☐

Action:
If ulcer(s) not treated or not healing with present treatment, refer to Community Nursing services.

50 *In the last year have you had knee pain for most days (more than 14) of any month?* Yes ☐ No ☐

51a *"Please can you show me the tablets or medicine that you are currently taking."* For each one ask, *"How many of these or how much do you take each day?*

Any tablets or medicines shown? Yes ☐ No ☐

Print from container

51b

Name of tablet, medicine etc	Total daily dosage	Units	Dosage as required	Units

51c Number of different medications:

0 1 2 3 4 5 6 7 8 9
10
1

51d **Check drug list for interactions.**
Are there any interactions?

Yes ☐
No ☐

Action:
If possible drug interaction, refer to team.

Thank you very much for your time and help. All I need to do now is take a blood test and check your urine".

Take blood and test urine (MSU if incontinent and stool specimen if necessary)

52 **Blood Test**

Has the patient been fasting (not eaten in the last 12 hours) before the blood sample was taken? Yes (Fasting) ☐ No ☐

Blood Constituent	**Patient Result**		**Refer to Team**	**Immediate Action (inform GP) (within 8 hours)**
Haemoglobin	☐☐.☐☐	g/dl	<9 or >18	<8.0
White cell count	☐☐☐	x 10^9/l	<3 or >16	<2 or >17
Platelets	☐☐☐☐	x 10^9/l	<100 or >900	<80
TSH	☐.☐☐	mU/l	<0.1 or >4	>16
Glucose	☐☐.☐☐	mmol/l	>7.5 (fasting) or >12 (not fasting)	>15
Sodium	☐☐☐	mmol/l	<129	<125 or >152
Potassium	☐☐.☐☐	mmol/l	<3.3	<3.0 or >6.0
Urea	☐☐	mmol/l	>18	>24
Creatinine	☐☐☐	mmol/l	>250	>350
Total protein	☐☐☐	g/l		
Albumin	☐☐	g/l	<30	<25
Calcium	☐.☐☐	mmol/l	<2.0 or >2.7	>2.8
Phosphate	☐.☐☐	mmol/l		
Bilirubin	☐☐	mmol/l	>35	>50
Alkaline phosphatase	☐☐☐☐	iU/l	>350	
AST	☐☐☐	iU/l	>80	>120
Uric acid	☐.☐☐	mmol/l	>0.8	

53

Dip stick results	Positive (record number of +s) +	++	+++	++++	Negative	Action if result is positive
Glucose	☐	☐	☐	☐	☐	Refer to team
Protein	☐	☐	☐	☐	☐	MSU
Blood	☐	☐	☐	☐	☐	MSU

54 **Where applicable:** MSU (tick appropriate box) Infected ☐ Not infected ☐

Immediate Action: If grossly infected, plus acute symptoms, inform GP within 8 hours.

Action: If infected, refer to team

55 **Where applicable:** Stool specimen

Report shows presence of occult blood Yes ☐ No ☐

Action: If occult blood present, refer to team.

56a Any other serious condition which, in the nurse's opinion needs further assessment? Yes ☐ No ☐

56b **If yes,** give details:

57a Are there any assessor's comments relevant to the assessment? Yes ☐ No ☐

57b **If yes,** give details:

Interview finish time (24 hour clock)

Hours: 0 1 2 / 3 4 5 6 7 8 9

Minutes: 0 1 2 3 4 5 / 6 7 8 9

Visit finish time (24 hour clock)

Hours: 0 1 2 / 3 4 5 6 7 8 9

Minutes: 0 1 2 3 4 5 / 6 7 8 9

Referral Agencies
(tick all that patient has been referred to)

- ☐ GEM/PCT
- ☐ Dentist
- ☐ Chiropodist
- ☐ Ophthalmologist
- ☐ Optician
- ☐ Audiometry
- ☐ Community Psychiatric Nurse
- ☐ Memory Clinic
- ☐ Continence Advisor
- ☐ Community Nursing Services
- ☐ Social Services
- ☐ Occupational therapist
- ☐ Dietician
- ☐ Other

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